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The Western Journal of Medicine

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ABSTRACTS JANUARY 1992

(Lewis CE, Montgomery K: Primary care physicians' refusal to care for patients infected with the human immunodeficiency virus. West J Med 1992 Jan; 156:36-38)

We conducted a telephone survey of a random sample of office-based primary care physicians in Los Angeles County to determine their practice experiences with patients infected with the human immunodeficiency virus (HIV). Telephone interviews included questions related to the physicians' experiences evaluating patients for HIV infection during the past 6 months and the presence of HIV-infected patients in their practices. Those without HIV-infected patients were asked if this was because they had not encountered such patients, because those patients had died, or because the physicians had chosen to refer these patients elsewhere or the patients had gone elsewhere for care. Of physicians who participated in the survey, 78% had evaluated a patient for HIV infection in the past 6 months; 34% were currently providing primary care for infected patients; and 36% had elected to refer HIV-infected patients elsewhere, or their patients had elected to find other physicians. In all, 48% of physicians in the sample had elected not to care for, or said they would not provide care for, patients with HIV infection.

Among Los Angeles County primary care physicians, 36% have refused to provide continuing care for HIV-infected patients and another 12% indicated their unwillingness to do so should such patients present themselves for care. As of 1991, the reservoir of primary care physicians in Los Angeles not yet involved with but willing to care for HIV-infected patients is relatively small (15%).

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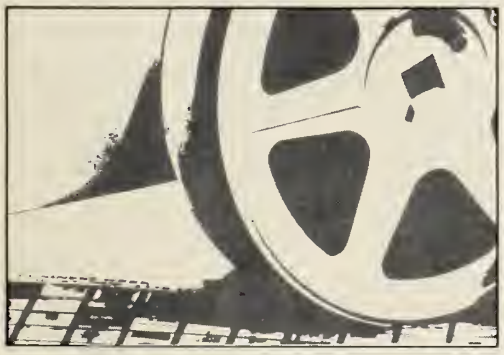

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150 mg b.i.d.

ACID TESTED. PATIENT PROVEN.

1. Data on file, Lilly Research Laboratories. *See accompanying page for prescribing information.* © 1991, ELI LILLY AND COMPANY NZ-2947-B-249304

AXID®

nizatidine capsules

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: 1. *Active duodenal ulcer*—for up to 8 weeks of treatment at a dosage of 300 mg h.s. or 150 mg b.i.d. Most patients heal within 4 weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a dosage of 150 mg h.s. at bedtime. The consequences of therapy with Axid for longer than 1 year are not known.

3. *Gastroesophageal reflux disease (GERD)*—for up to 12 weeks of treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn at a dosage of 150 mg b.i.d.

Contraindication: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups.The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of anti-androgenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

PV 2093 AMP [101591]

Additional information available to the profession on request.

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FREE HIV RISK ASSESSMENT PROGRAM AVAILABLE

CMA's Department of Physician Education has produced a new CME program, "HIV Risk Assessment: Methods and Guidelines," which is available free to physicians. This program teaches effective strategies developed by expert physicians to identify patients who are potentially at risk for HIV infection. Worth one hour of CME Category I credit, the program is designed for groups of 5-20 physicians.

The program features CMA's award-winning, 11-minute video, "Let's Talk," which highlights several methods physicians can use to perform HIV assessment with patients. Participants receive a course outline, camera-ready slide reproductions, a compilation of state laws pertaining to HIV/AIDS, community resource guide to HIV testing and counseling, risk assessment guidelines, and a model HIV consent form and patient information pamphlet.

Those interested in taking part in this unique CME program should contact Amy Wright in CMA's Department of Physician Education at 415/882-5186.

LET'S TALK
ABOUT AIDS RISK

ABSTRACTS JANUARY 1992

(Zeldis JB, Jain S, Kuramoto IK, et al: Seroepidemiology of viral infections among intravenous drug users in northern California. West J Med 1992 Jan; 156:30-35)

Intravenous drug users are frequently exposed to parenterally transmitted viral infections, and these infections can spread to the general population through sexual activity. We investigated the prevalence of serologic markers for human immunodeficiency virus type 1 (HIV-1), human T-cell lymphotropic virus type I/II (HTLV-I/II), hepatitis B virus (HBV), and hepatitis C virus (HCV) in intravenous drug users and their sexual contacts. Of 585 drug users from northern California tested for these serologic markers, 72% were reactive for the antibody to HCV, 71% for the antibody to hepatitis B core antigen, 12% for HTLV-I/II antibodies, and 1% for the HIV-1 antibody. The prevalence of serologic markers for these four viruses correlated with the duration of intravenous drug use, the ethnic group, and the drug of choice. More than 85% of subjects infected with either HCV or HBV were coinfected with the other virus. All persons reactive to HTLV-I/II antibodies had antibodies for either HBV or HCV. Of 81 sexual contacts tested, 17% had evidence of HBV infection while only 6% were reactive for HTLV-I/II antibodies and 4% for the antibody to HCV. None of this group was infected with HIV-1.

We conclude that HTLV-I/II and HCV are inefficiently transmitted to sexual contacts while HBV is spread more readily. Programs designed to discourage the sharing of drug paraphernalia, such as needle and syringe exchanges, should decrease the risk of parenterally spread viral infections in intravenous drug users and thus slow the spread of these infections to the general population.

IV DRUG USE HEPATITIS B VIRUS HEPATITIS C VIRUS
HIV VIRAL EPIDEMIOLOGY
HTLV-I/II SEXUALLY TRANSMITTED DISEASE

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HIV VIRAL EPIDEMIOLOGY
HTLV-I/II SEXUALLY TRANSMITTED DISEASE

Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

Non-surgical treatment for even the most advanced venous ulcers.

The physicians at Vein Clinics of America have successfully treated venous leg ulcers—including advanced cases—in our offices without the use of surgical procedures.

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Rapid closing of ulcer.

The common denominator of most leg ulcers is venous pump failure with edema. Our treatment first removes the edema and heals the ulcer through the application of isometric compression bandaging. This increases venous outflow during ambulation, resulting in improved pump action at the calf muscle.

Healing occurs in three to six weeks for most patients, or longer in more advanced cases. Other advantages of this phase include immediate ambulation, rapid elimination of pain and drainage and high patient acceptance.

D.K., a 69-year-old woman with recurrent ulcer and history of skin graft failures, on initial day of treatment. Edema of ankle and inflammation clearly visible.

Effective long-term healing.

Once the ulcer has healed and other problems such as edema and dermatitis are under control, the second phase of treatment can address prevailing underlying causes. Refluxing venous trunks, tributaries and incompetent perforating veins are eliminated by injection compression sclerotherapy, often guided by Duplex Color Ultrasound.

This selective fibrosis process improves the venous pump, resulting in long-term healing and lowered recurrence of leg ulcers.

Proven treatment program with documented results.

This treatment protocol was developed over 10 years of clinical experience, with favorable results on approximately 500 leg ulcer patients.

Many patients had previous surgery with skin grafting and vein stripping. But our two-step protocol provided more effective healing. This is because the treatment is directed at the underlying cause, the venous pump failure.

For information on how your patients can benefit from this treatment call Allan Ebbin, MD, Western Region Medical Director at (714) 889-0502.

After 17 days of isometric dressing application, ulcer is responding.

Progressive granulation and healing of ulcer. Considerable reduction of edema in subcutaneous tissues.

Long-term follow-up, including injection therapy shows no edema or ulceration.

Results Achieved Without Surgery

Vein Clinics of America

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The Western Journal of Medicine

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EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

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Items of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently became reasonably firmly established, both as to scientific fact and important clinical significance.

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DAVID A. LEWIS, MD, and DARRYL Y. SUE, MD

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Calan® SR

verapamil HCl 180 mg

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The recommended starting dose for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control.

A lower initial starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature).

Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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Medical & Scientific
Information Department
4901 Searle Parkway
Skokie, IL 60077

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 18-19—**1st Annual Current Topics in Anesthesiology.** Mayo Clinic-Scottsdale at Ritz Carlton, Phoenix. Sat-Sun. Contact: Trish Gean, (602) 391-8300.

January 25—**Scottsdale Asthma Conference.** Scottsdale Memorial Hospital, Greater Phoenix Allergy Society, Tucson Allergy Society, and Arizona Allergy Society at the Scottsdale Plaza Resort, Scottsdale. Sat. Contact Merle Scherr, MD, (602) 994-9514.

January 27-31—**20th Annual Surgical Symposium.** Maricopa Medical Center and Phoenix Surgical Society at Scottsdale Hilton, Scottsdale. Mon-Fri. Contact: Marilyn Garter, (602) 266-6321.

January 27-31—**Psychopharmacology Review: Current Clinical Practice.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Mon-Fri. Contact: U of A.

January 30-February 1—**17th International Conference on Stroke and Cerebral Circulation.** American Heart Association at Phoenix. Fri-Sun. Contact: C. MacDonough, (214) 706-1441.

February 6-9—**Medical Acupuncture in 1992: Elegance and Clinical Excellence in Pain Management.** University of Arizona College of Medicine at Scottsdale Hilton Resort and Spa, Scottsdale. Thurs-Sun. Contact: (213) 937-5514.

February 14-16—**Anesthesia for the '90s: 18th Annual Scientific Meeting.** University of Arizona College of Medicine at Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Beverly Richter, (602) 246-8901.

February 20-22—**18th Annual Frontiers in Ophthalmology.** St Luke's Medical Center at Red Lion's LaPosado Resort, Scottsdale. Thurs-Sat. Contact: Christine Campbell, (602) 820-7027.

February 24-27—**Practical Radiology.** University of Arizona College of Medicine at Loews Ventana Canyon Resort, Tucson. Mon-Thurs. Contact: U of A.

February 25-28—**14th Annual Tucson Hospitals Medical Education Medical Conference—Clinical Update.** Cascade Village, Durango, Colorado. Tues-Fri. Contact: Richard Dale, MD, (602) 885-2303.

February 27-28—**Advances in Obstetrics and Gynecology.** Maricopa Medical Center and Phoenix OB/GYN Society at Scottsdale Hilton, Scottsdale. Wed-Fri. Contact: Marilyn Harter, (602) 266-6321.

February 27-29—**Geriatric Medicine Update and Board Certification Review Course.** University of Arizona College of Medicine at Doubletree Hotel, Tucson. Thurs-Sat. Contact: U of A.

February 27-March 1—**Teaching Each Other—Arizona Academy of Family Physicians 43rd Annual Scientific Assembly.** Wyndham Paradise Valley Resort, Scottsdale. Thurs-Sun. Contact: Jerry Davis, (602) 249-2021.

June 4-6—**Arizona Medical Association—Annual Meeting.** Scottsdale. Thurs-Sat. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For more information on accreditation or certification, please write to the above address.

ALLERGY

February 6-8—**Allergy Diagnosis.** UCSD at La Jolla Village Inn. Thurs-Sat. 20 hrs. $290. Contact: Janice Turner, PO Box 2586, La Jolla 92038. (619) 459-1564.

March 27-28—**Asthma and Allergy in the 1990s.** Medical Education Resources at Wyndham Hotel, Palm Springs. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

ANESTHESIOLOGY

January 19-21—**Second America-Japan Anesthesia Congress.** International Anesthesia Research Society at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sun-Tue. 14 hrs. $250. Contact: Vicky Larsen, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132. (801) 581-6115.

January 19-24—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

January 24-26—**30th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital of Los Angeles at Stouffer Concourse Hotel. Fri-Sun. 15 hrs. Contact: Katherine Barky, MD, PO Box 54700, Los Angeles 90054. (213) 669-2262.

March 13-17—**66th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at San Francisco Hilton & Towers. Fri-Tues. Contact: Anne Maggiore, IARS, 2 Summit Park Dr, Ste 140, Cleveland, OH 44131. (216) 642-1124.

March 21-22—**Postgraduate Assembly.** Los Angeles County Society of Anesthesiologists at Sheraton Universal Hotel, Universal City. Sat-Sun. Contact: Michael Carlson, 1903 Redondo Ave, Long Beach 90804. (213) 597-2661.

March 21-26—**20th Obstetric Anesthesia Conference.** Ohio State University Hospitals at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

May 17-22—**Anesthesiology Review Course.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

CARDIOLOGY

January 15—**21st Annual Respiratory Symposium.** Enloe Hospital and Chico Community Hospital at Esplanade Bldg Enloe Hospital, Chico. Wed. Contact: Linda Spring, (916) 891-7375.

January 18-25—**Cardiopulmonary Emergencies.** UCSD at Kona, Hawaii. 1 week. Contact: UCSD.

February 12—**32nd Annual Cardiology Symposium.** Enloe Hospital and Chico Community Hospital at Esplanade Bldg Enloe Hospital, Chico. Wed. Contact: Linda Spring, (916) 891-7375.

February 14-16—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

(Continued on Page 16)

Dr. Craig Watson
Medical Director, Sutter Neuroscience Center
Sutter General Hospital

YOU CAN'T WATCH YOUR EPILEPSY PATIENTS ROUND-THE-CLOCK. BUT WE CAN.

Even if you've made a positive diagnosis of epilepsy in patients who are suffering from seizures, the most effective treatment is sometimes elusive.

The reason? Most physicians never directly observe a seizure. The patient usually recalls little, and second-hand accounts from family and friends are sketchy.

Sutter Neuroscience Center at Sutter General Hospital offers a comprehensive in-patient program for epilepsy that permits precise diagnosis and treatment.

Patients are monitored 24-hours a day by both video cameras and an EEG. When a seizure occurs, all relevant data can be recorded and studied. Treatment decisions, including medication and/or surgery, can then be based on specific information.

The four-bed unit, which is the largest and most complete in the region, is designed for the comfort of the patients, who may need to be hospitalized for up to a week. Rooms are outfitted with a television, VCR and personal exercise equipment.

The program is designed for patients aged fifteen and older who have tried several different anti-convulsant medications, yet continue to experience seizures that interfere with their quality of life.

Most insurance plans cover the costs. Once patients complete the program, they are returned to their primary care physician with follow-up recommendations.

For more about services or patient transfers, call Sutter Neuroscience Center at Sutter General Hospital in Sacramento, (916) 455-4323.

Sutter Neuroscience Center

(Continued from Page 14)

March 20-21—**Cardiac Diagnostic Methods & Risk Management.** Medical Education Resources at Caesars Palace, Las Vegas, Nevada. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

April 4—**Practical Cardiology for the '90s.** Grossmont Hospital at La Mesa. Sat. Contact: Karen Hamilton, PO Box 158, La Mesa 91944-0158. (619) 589-4168.

April 6-11—**31st Annual Cardiology Retreat.** Scripps Clinic and Research Foundation at Rancho Santa Fe. Mon-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 21-23—**2nd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 1-2—**2nd International Symposium on Thrombolytic Therapy in Acute Ischemic Stroke.** Scripps Clinic and Research Foundation at San Diego Marriott, La Jolla. Fri-Sat. Contact: Scripps Clinic, Box 403C, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

CRITICAL CARE

February 3-7—**Critical Care Medicine.** USC at Caesar's Palace, Las Vegas, Nevada. Mon-Fri. 33.5 hrs. $695. Contact: USC.

DERMATOLOGY

January 17-19—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

January 31-February 2—**Cutaneous Malignancies: 1992 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 18 hrs. Contact: Susan Buntjer, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

February 27—**Problems of the Aging Skin.** Stanford Medical Center at Palm Springs. Thurs-Sun. Contact: Pamela Bain, R-144, Stanford 94305. (415) 723-7854.

EMERGENCY MEDICINE

January 13-17—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. Contact: UCSD.

February 23-28—**Emergency Medicine.** UCD at Incline Village, Nevada. Sun-Fri. Contact: UCD.

March 8-13—**13th Annual Mammoth Mountain Emergency Medicine Ski Conference.** CAL/ACEP and Orange County Emergency Department at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Mark Song, Medical Conferences, PO Box 52-B, Newport Beach 92662. (714) 552-0831.

March 16-20—**Emergency Medicine Symposia II.** UCSD at Basic Science Building. Mon-Fri. Contact: UCSD.

March 20-21—**Advances in Emergency Medicine: Toxicology and Infectious Diseases.** UCLA at Hotel del Coronado. Fri-Sat. 13.5 hrs. $125. Contact: UCLA Extension.

April 1-4—**8th Annual Advances in Emergency Medicine.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Sat. $455. Contact: UCSF.

May 6-10—**14th Biannual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 18 hrs. $200-$435. Contact: UCSD.

May 11-15—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. Contact: UCSD.

June 22-26—**Emergency Medicine Symposia III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. Contact: UCSD.

ENDOCRINOLOGY AND METABOLISM

March 4-5—**Advances in Endocrinology and Metabolism.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Thurs. 14.5 hrs. $295. Contact: UCSF.

March 6—**18th Annual Diabetes Symposium.** UCD at Sacramento. Fri. 6 hrs. $140. Contact: UCD.

March 6-7—**Diabetes Update.** UCSF at Pan Pacific Hotel, San Francisco. Fri-Sat. 10 hrs. $245. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

January 31-February 1—**3rd Annual Pediatric Dermatology for the Primary Care Physician.** UCSF at Le Meridien, San Francisco. Fri-Sat. 10.5 hrs. $255. Contact: UCSF.

February 9-15—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Marriott Hotel, Newport Beach. Sun-Sat. Contact: UCI.

February 13-15—**Current Concepts in Cancer Management: A Symposium for Primary Care Physicians and Cancer Care Providers.** Hoag Memorial Center at Newport Beach Marriott. Thurs-Sat. $350. Contact: Meeting Management, 5665 Oberlin, Ste 110, San Diego 92121. (619) 453-6222.

February 13-16—**44th Annual Scientific Assembly.** California Academy of Family Physicians at Sheraton Harbor Island Hotel, San Diego. Thurs-Sun. 26 hrs. $275. Contact: Robert Fagan, CAFP, 114 Sansome St, Ste 1305, San Francisco 94104. (415) 394-9121.

February 14-16—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 17-19—**Issues in Men's Health.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 29—**Dermatology for the Primary Care Physician.** UCLA at Biltmore Hotel, Los Angeles. Sat. 5.5 hrs. $55. Contact: UCLA Extension.

March 25-27—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF. Wed-Fri. 15.5 hrs. Contact: UCSF.

April 4—**Cardiology for Primary Care.** UCDMC at Cancer Center Auditorium. Sat. Contact: UCD.

April 4-11—**5th Annual Primary Care Medicine: Update 1992.** UCSF at Maui Intercontinental, Wailea, Maui, Hawaii. 1 week. $540. Contact: UCSF.

April 9-11—**Advances in Rheumatology for Primary Care Physicians.** UCSF at Le Meridien Hotel, San Francisco. Thurs-Sat. $240. Contact: UCSF.

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Annual Session and | Western Scientific Assembly | March 13-18, 1992 Disneyland Hotel Anaheim, CA

California Medical Association

CALIFORNIA MEDICAL ASSOCIATION'S
Annual Session and Western Scientific Assembly

March 13 - 18, 1992 • Disneyland Hotel, Anaheim, CA

The 1992 Western Scientific Assembly promises an outstanding lineup of 36 provocative programs, most of which have been approved for full CME Category I credit! The list of rich and varied topics include surviving malpractice litigation, coronary artery disease, breast cancer, treatment of low back pain, management of headache, skin cancer recognition and treatment, effects of secondhand smoke, clinical opportunities to prevent injury, controversies in pharmacotherapy of asthma, futile medical treatment, the physicians' role in working with the handicapped and disabled, update on osteoporosis, pediatric infectious diseases and patients who try physicians' patience. In addition, workshops will be offered in cardiac life support and suture procedures.

House of Delegates will set CMA policy on health care issues facing physicians.

For complete program and registration information call (415) 882-3384 or MAIL this form to: California Medical Association, Attention: Anna Durante, P.O. Box 7690, San Francisco, CA 94120-7690

Name _____

Address _____

City _____

State _____ Zip _____

Hospital Medical Staff Section and **Young Physicians Section** will convene their annual meetings.

Technical Exhibits will feature medical and other health care related exhibits.

Special Events will include a tour of Universal Studios and Hollywood, Laguna Arts and Antiques, Whale Watching and much more.

(Continued from Page 16)

April 10-12—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Vacation Village, San Diego. Fri. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 15-20—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Marriott Hotel, Newport Beach. Mon-Sat. Contact: UCI.

GASTROENTEROLOGY

February 29-March 1—**Endoscopy Update 1992.** Southern California Society for Gastroenterology at Century Plaza Hotel, Los Angeles. Sat-Sun. Contact: Joyce Fried, University of California Brain Research Institute, Los Angeles 90024.

GERIATRICS

January 21-25—**9th UCLA Intensive Course in Geriatric Medicine.** UCLA at Beverly Hilton. Tues-Sat. 40 hrs. $600. Contact: UCLA.

January 24-25—**Alzheimer's Disease: New Approaches to Treatment.** UCSD at Westgate Hotel, San Diego. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 6-8—**Recent Advances in Geriatric Medicine-Healthy People 2000: A New Look at Screening, Prevention and Rehabilitation in the Elderly.** UCSD at Pan Pacific Hotel, San Diego. Fri-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 16-17—**Exercise in Geriatric Care.** VA Sepulveda Medical Center at Burbank. Mon-Tues. Contact: Symposium Secretary, VA Medical Center, GRECC (11E), 16111 Plummer St, Sepulveda 91343. (818) 895-9311.

INFECTIOUS DISEASES

February 7-8—**10th Annual Practical Update of Infectious Disease.** UCD. Fri-Sat. 12 hrs. $160. Contact: UCD.

April 25—**HIV Update.** UCDMC at Cancer Center Auditorium. Sat. Contact: UCD.

April 29-May 1—**13th Annual Advances in Infectious Diseases.** UCSF at San Francisco. Wed-Fri. $400. Contact: UCSF.

May 6-8—**13th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. $400. Contact: UCSF.

INTERNAL MEDICINE

January 30-February 1—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott, San Diego. Thurs-Sat. 17 hrs. $350. Contact: UCSD.

January 31-February 2—**State of the Art Urology.** UCLA at Ritz-Carlton, Marina del Rey. Thurs-Sat. 20.5 hrs. $350. Contact: UCLA Extension.

February 22-27—**Topics and Advances in Internal Medicine.** UCSD at Sheraton Harbor Island, San Diego. Sat-Sun. Contact: UCSD.

February 23-25—**5th Annual Congress of the North American Society of Phlebology on the Advances in Sclerotherapy and the Advances in Surgical and Medical Treatment of Venous Disease.** North American Society of Phlebology and the American Academy of Dermatology at Grand Hyatt Union Square, San Francisco. Sun-Tues. 14 hrs. Contact: NASP, 204 N El Camino Real, E-234, Encinitas 92024. (619) 942-8380.

February 27-29—**1992 Zimmerman Conference: Progress in Vascular Biology, Hemostasis and Thrombosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 20-26—**Internal Medicine 1992: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado. Fri-Thurs. 54 hours. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

May 11-15—**20th Annual Advances in Internal Medicine.** UCSF at Ritz-Carlton Hotel, San Francisco. Mon-Fri. 33 hrs. $610. Contact: UCSF.

June 22-26—**20th Annual Advances in Internal Medicine.** UCSF at Cole Hall Parnassus Campus. Mon-Fri. 32 hrs. $610. Contact: UCSF.

NEUROLOGY

January 30-February 1—**15th Annual: Neurology for Non-Neurologists.** UCSD at Omni San Diego Hotel. Thurs-Sat. 21 hrs. $375. Contact: UCSD.

February 13-15—**25th Annual Recent Advances in Neurology.** UCSF at San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

OB/GYN

January 16-19—**OB/GYN and Ultrasound.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 20 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 2-6—**Ambulatory Gynecology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

February 13-16—**47th Annual Postgraduate Assembly.** OB/GYN Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB/GYN Assembly, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

April 2-4—**Gynecologic Surgery.** Memorial/UCI Center for Health Education at Marquis Hotel, Palm Springs. Thurs-Sat. Contact: UCI.

April 2-4—**Ultrasound Update.** Memorial/UCI Center for Health Education at Bally's Hotel, Las Vegas. Thurs-Sat. Contact: UCI.

April 8-12—**Pacific Coast Fertility Society: Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Director of Medical Education, 12760 La Mirada Blvd, Ste 220, La Mirada 90638. (213) 947-7068.

June 5-7—**Advanced Fetal Heart Rate Monitoring.** Memorial/UCI Center for Health Education at Radisson Hotel, Palm Springs. Fri-Sun. Contact: UCI.

OCCUPATIONAL/ENVIRONMENTAL

January 27-February 7—**Occupational and Environmental Medicine Series: Session I.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

February 10-14—**Occupational and Environmental Medicine: Session III.** UCSF at Miyako Hotel Japan Center, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

February 12-16—**Team Physician Course.** American College of Sports Medicine at Wyndham Hotel, Palm Springs. Wed-Sun. Contact: ACMS, PO Box 1440, Indianapolis, IN 46202-1440. (317) 637-9200.

ONCOLOGY

February 17-19—**Clinical Hematology and Oncology: 1992.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. $385. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 29—**Neo Adjuvant Approach to Non-Small Cell Lung Cancer.** UCD at Incline Village, Nevada. Sat. Contact: UCD.

March 5-7—**7th International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at San Diego Marriott. Thurs-Sat. Contact: UCSD.

April 30-May 3—**Breast Cancer Conference.** Memorial/UCI Center for Health Education at Hyatt Regency, Long Beach. Thurs-Sun. Contact: UCI.

OPHTHALMOLOGY

January 31-February 4—**11th Annual Squaw Valley Retina Symposium.** Alta-California Ophthalmological Society at Resort at Squaw Creek, Olympic Valley. Fri-Tues. 16 hrs. Contact: Richard Murray, 2701 Eye St, Sacramento 95816. (916) 442-4975.

March 6-7—**6th Annual Visions in Ophthalmology: '92.** Scripps Memorial Hospital at Mericos Eye Institute. Fri-Sat. Contact: Meeting Management, (619) 453-6222.

March 12-13—**Ophthalmology in Developing Countries: An International Symposium.** UCSF at Holiday Inn, San Francisco. Thurs-Fri. 15 hrs. $350. Contact: UCSF.

May 15-16—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 403C, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

ORTHOPEDICS

January 23-25—**Orthopaedic Update II: Current Concepts and Advances.** UCSD at Hyatt Islandia Hotel, San Diego. Thurs-Sat. Contact: UCSD.

(Continued on Page 22)

Come to San Diego for...

Advances In Internal Medicine: 1992

American College of Physicians
73rd Annual Session
March 26-29, 1992

Pre-Session Courses
March 24-25, 1992

Broaden your understanding and refresh your knowledge of internal medicine and its related subspecialties in over 300 scientific sessions. PLUS, explore this year's curriculum on Men's and Women's Health Issues, covering such topics as:

- Breast Cancer
- Hormone Replacement during Menopause
- Prostatic Cancer
- Sexually Transmitted Diseases...and more.

Pre-Registration Deadline:
February 24, 1992

For information on registering, call our Registration Hotline: 800-523-1546, ext. 2429 or dial direct 215-351-2429.

How to Register

ACP Membership: Consult your Advance Program mailed in December. It contains information about the meeting and how to register.

Nonmembers: Watch for the complete schedule of events and a registration form in the Annual Session Digest appearing in the December 15, 1991, and January 1 and February 1, 1992, issues of *Annals of Internal Medicine.*

A|C|P

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★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

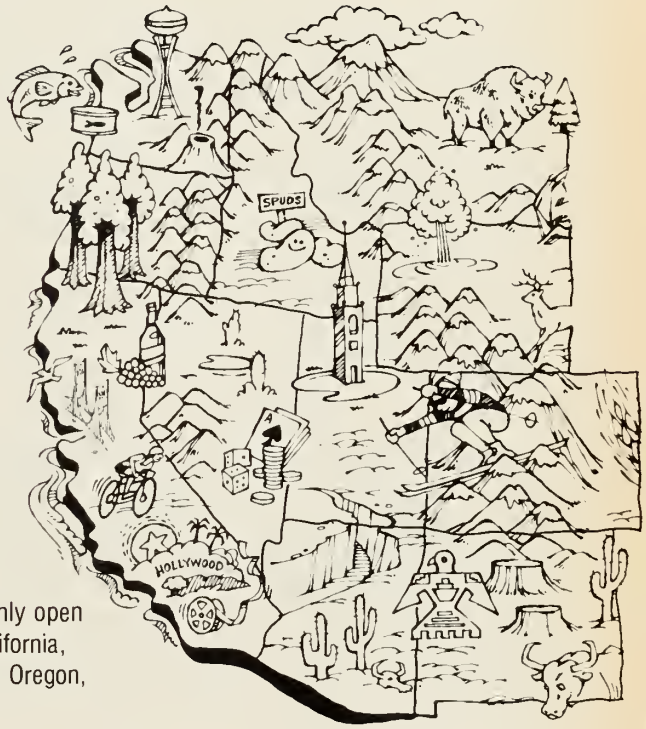
★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

The Western Journal of Medicine

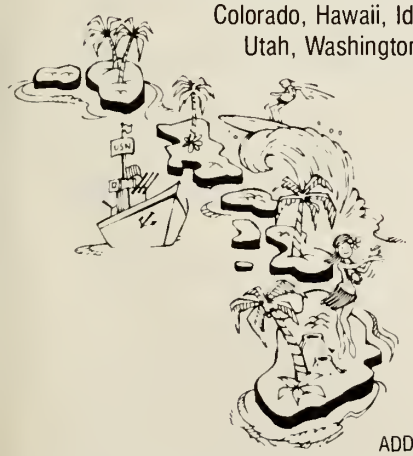
Medical Student 1992 Writing Award Competition

$1,000 CASH PRIZE!

■ Enter your original medical research or medical review article—the article must be of interest to clinicians and not previously published. The winner will receive a $1,000 cash prize and a two-year subscription to **The Western Journal of Medicine.** The winning article will be published in **WJM. Deadline to enter, March 1, 1992.**



■ **WJM** is the official journal of ten western medical associations and six clinical investigation/specialty societies. This competition is only open to medical students attending school in Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, or Wyoming.



■ **WJM** is clinically oriented, national in scope, and not confined to any single specialty. Your article must be written in **WJM** style and be of interest to our readers. If, in the judgment of the editorial board, no articles meet the standards of **WJM,** no award will be made.

ADDITIONAL RULES:

■ Articles must be 3,000 to 4,000 words in length. The manuscript must be identified as submitted for consideration for this award.

■ Co-authorship is permitted if all authors meet the qualifications. The $1,000 award will be divided equally among the co-authors.

■ Articles must conform to **WJM's** style—our style guide, "Instructions for Authors," appears in the January and July issues, or you may write our editorial department for a copy of the guide.

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Editorial Office/Award Competition
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CONTINUING MEDICAL EDUCATION

(Continued from Page 18)

January 23-26—**Fracture Management.** UCD at Resort at Squaw Creek, Squaw Valley. Thurs-Sun. Contact: UCD.

March 15-20—**The Spine: Current Concepts of Diagnosis and Treatment.** Vanderbilt University Medical Center Department of Orthopaedics at Grand Hyatt Wailea, Maui, Hawaii. Sun-Fri. $575. Contact: The Spine/Current Concepts, c/o Unconventional Inc, 3960 Park Blvd, Ste E, San Diego 92103. (619) 692-9115.

PAIN MANAGEMENT

February 19-22—**The Practicing Physician's Approach to the Difficult Headache Patient.** University of Chicago School of Medicine at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 878-0396.

PATHOLOGY

January-May 1992—**Bay Area Seminars in Cytopathology: 1992.** UCSF at Health Sciences West on Campus. Thursdays. 10 hrs. $150. Contact: UCSF.

February 24-26—**Fine Needle Aspiration Basic Tutorial.** UCSF at Squaw Valley. Mon-Wed. 12 hrs. $850. Contact: UCSF.

February 27-29—**Fine Needle Aspiration Advanced Tutorial.** UCSF at Squaw Valley. Thurs-Sat. 12 hrs. $850. Contact: UCSF.

April 11—**7th Annual Conference: New Treatment in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 16—**Fine Needle Aspiration Basic Tutorial.** UCSF. Sat. 12 hrs. $650. Contact: UCSF.

May 21-22—**Curent Issues in Anatomic Pathology: 1992.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Fri. 13 hrs. $325. Contact: UCSF.

PEDIATRICS

January 22-25—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Hyatt Regency Hotel, La Jolla. Wed-Sat. Contact: Children's Hospital, 8001 Frost St, San Diego 92123. (619) 495-4940.

February 7-9—**Current Concepts in Pediatric Medicine: 1992.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 18 hrs. Children's Hospital, (619) 576-4072.

March 4-6—**17th Annual Care of the Sick Newborn.** Memorial/UCI Center for Health Education at Long Beach. Wed-Fri. Contact: UCI.

April 24-26—**1992 West Coast Regional Conference on Pediatric Psychology.** UCSF at Union Square Holiday Inn, San Francisco. Wed-Fri. Contact: UCSF.

May 14-16—**25th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $325. Contact: UCSF.

June 26-28—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Wed-Fri. Contact: Continuing Education, (619) 576-4072.

PSYCHIATRY

January 26-31—**18th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 1-3—**West Coast Neuropsychological Assessment Conference: Recent Advances in the Boston Approach to Neuropsychological Assessment.** UCSD at Pan Pacific Hotel, San Diego. Sun-Mon. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 8-9—**Breakthroughs in Anxiety Disorders: Treating Anxiety, Panic and Obsessive-Compulsive Disorders and Depression.** UCSD at Omni Hotel, San Diego. Sat-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 15-16—**Victims of Abuse: The Emotional Impact of Child and Adult Trauma.** San Diego Psychoanalytic Society and Institute at Hyatt Regency La Jolla at Aventine. Sat-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 13-15—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at US Grant Hotel, San Diego. Fri-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

April 10-11—**The Cutting Edge 1992: Erotic Mysteries—Intimacy, Sexuality and Gender in the '90s.** UCSD at Omni Hotel, San Diego. Fri-Sat. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

April 10-14—**The Power of the Art—Suggestive Therapeutics: An Introduction to Medical Hypnosis.** UCSD at Mission Bay Hilton, San Diego. Fri-Tues. Contact: UCSD.

April 23-24—**11th Annual Conference on Child Abuse and Neglect.** UCDMC at Radisson Hotel, Sacramento. Thurs-Fri. 12 hrs. $175. Contact: UCD.

RADIOLOGY

January 26-31—**Advances in Neuro and Musculoskeletal MRI.** UCSF at Ritz-Carlton, Mauna Lani, Hawaii. Sun-Fri. 23.5 hrs. $595. Contact: UCSF.

January 31-February 2—**44th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 17.25 hrs. $425. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 3-7—**Magnetic Resonance Imaging in the Desert.** UCSF at Ritz-Carlton, Rancho Mirage. Mon-Fri. 22.5 hrs. $595. Contact: UCSF.

February 4-7—**Advanced Seminars in Diagnostic Imaging.** UCSD at Le Meridien Hotel, Coronado. Tues-Fri. 20 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 4-8—**18th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Hyatt Regency Waikoloa, Hawaii. Tues-Sat. 18.5 hrs. $550. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 10-13—**Mammographically Detected Early Breast Cancer.** University of Alabama at Birmingham at Ritz-Carlton, Rancho Mirage. Mon-Thurs. 18 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 24-28—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI and Interventional.** Stanford University Medical Center at Ritz-Carlton Mauna Lani, Hawaii. Mon-Fri. 23.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 27-29—**Head and Neck Imaging: Total Immersion.** UCSF at Ritz-Carlton, Rancho Mirage. Thurs-Sat. 14 hrs. $325. Contact: UCSF.

February 27-30—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Thurs-Sun. 20 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 2-6—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27.25 hrs. $540. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 11-13—**12th Annual Current Approaches to Radiation Oncology, Biology, and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $375. Contact: UCSF.

March 13-15—**OB/GYN and Abdominal Sonography: Update 1992.** UCSF at Ritz-Carlton, San Francisco. Fri-Sun. 16 hrs. $395. Contact: UCSF.

March 21-23—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. 15 hrs. $350. Contact: UCSF.

March 22-27—**MRI Workshop in Hawaii: 1992.** Queens Medical Center at Kea Lani Hotel, Wailea, Hawaii. Sun-Fri. 37 hrs. $595. Contact: Susan Block, Queens Medical Ctr, 1301 Punchbowl St, Honolulu, HI 96813. (808) 547-4544.

April 5-10—**General Radiology Review Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sun-Fri. 40 hrs. $425. Contact: UCLA.

April 19-24—**Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $470. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 25—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $125. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

May 4-8—**MRI: A State of the Art Clinical Review.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Mon-Fri. 23.5 hrs. $540. Contact: UCSD.

May 8-10—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 15 hrs. $400. Contact: UCSD.

May 21-24—**Doppler and Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Thurs-Sun. 21.5 hrs. Contact: UCSD.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 22)

REHABILITATIVE/THERAPEUTIC

March 5-7—**Rehabilitation: Science, Technology, Quality and Costs—Present and Future.** Scripps Memorial Hospital at La Jolla Marriott. 18.5 hrs. $395. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

SLEEP MEDICINE

January 30-31—**New Horizons in Sleep Disorders Medicine.** California Thoracic Society at Doubletree Resort, Palm Springs. Thurs-Fri. Contact: California Thoracic Society, 202 Fashion Ln, #219, Tustin 92680. (714) 730-1944.

April 3-4—**Pharmacotherapeutics in Clinical Sleep Medicine.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

SURGERY

January-May 1992—**Temporal Bone Surgical Dissection Courses.** House Ear Institute at Los Angeles. 6 days each. 53 hrs. $1100. Contact: Antonio De la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext 7079.

January 17-18—**What's New in General Surgery.** UCD at Radisson Hotel, Sacramento. Fri-Sat. 16 hrs. $295. Contact: UCD.

February 8-11—**International Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery at Century City J W Marriott, Los Angeles. Sat-Tues. Contact: Sharon Clawson, (213) 278-8823.

February 9-14—**15th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. Contact: UCSD.

February 12-14—**2nd International Lung Transplant Symposium: Update 1992.** Cedars-Sinai Medical Center at Ritz-Carlton, Laguna Niguel. Wed-Fri. 6.5 hrs. $500. Contact: Carolyn Lavitt, Continuing Education, 8700 Beverly Blvd, Los Angeles 90048. (213) 855-5547.

February 29-March 1—**Renal Transplantation in the 1990s.** Sharp Memorial Hospital at Four Seasons Hotel, Newport Beach. Sat-Sun. 9 hrs. $175. Contact: Sharp Memorial Hospital, 7901 Frost St, San Diego 92123. (619) 541-4530.

March 18-21—**Surgical Challenges in the Head and Neck: A Dissection Course Emphasizing Contemporary Strategies.** UCSD at Basic Science Bldg, La Jolla. Wed-Sat. Contact: UCSD.

March 19-22—**42nd Annual Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: SGS, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

March 26-28—**Symposium on Aesthetic Surgery of the Face.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 18 hrs. $800. Contact: UCSF.

April 2-3—**General Thoracic Surgery.** American College of Chest Physicians at Caesar's Palace Hotel, Las Vegas, Nevada. Thurs-Fri. 13 hrs. $325. Contact: ACCP, PO Box 93826, Chicago, IL 60673. (800) 343-2227.

April 2-4—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. Contact: UCSF.

April 2-4—**12th Annual Meeting and Scientific Sessions of the International Society for Heart Transplantation.** UCSD at San Diego Marriott. Thurs-Sat. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

January 25-27 and March 1-2—**Lactation Educator Training Programs.** UCLA at Loma Linda. 22.5 hrs. $725. Contact: UCLA.

February 24-28—**Physician Heal Thyself.** UCSD at San Diego Princess Resort. Mon-Fri. Contact: UCSD.

February 28-29—**Nutrition: A Key Partner in the Treatment of Frequently Encountered Medical Problems.** UCD at Walnut Creek. Fri-Sat. Contact: UCD.

March 12-13—**Dimensions of Caring 1992: Enhancing Quality of Life in Palliative Care.** Scripps Clinic and Research Foundation at Omni Hotel, San Diego. Thurs-Fri. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 2-4—**Medicine Today.** UCSD at Price Center. Thurs-Sat. Contact: UCSD.

April 9-13—**Lactation Educator Training Programs.** UCLA at Westwood. 22.5 hrs. $725. Contact: UCLA.

(Continued on Page 95)

BuSpar®(buspirone HCl)

References: 1. Feighner JP, Cohn JB. Analysis of individual symptoms in generalized anxiety--a pooled, multistudy, double-blind evaluation of buspirone. *Neuropsychobiology* 1989;21:124-130. **2.** Newton RE, Marunycz JD, Alderdice MT, Napolitello MJ. Review of the side-effect profile of buspirone. *Am J Med* 1986;80 (suppl 3B):17-21. **3.** Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82 (suppl 5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: *General*—*Interference with cognitive and motor performance.* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity, however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding, and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice, buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B. Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea, miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials. *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients, infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: Signs and Symptoms—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

MJL8-4270R2

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▲ No more sedation (10%) than seen with placebo (9%)[2]

▲ Nonaddictive, no evidence of withdrawal syndrome[3]

▲ More commonly observed untoward events include dizziness (12%), nausea (8%), headache (6%), and nervousness (5%)

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Please see references and brief summary on adjacent page.

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Biomedical Science

Indoor Radon and Lung Cancer
Estimating the Risks

JONATHAN M. SAMET, MD, *Albuquerque, New Mexico*

Radon is ubiquitous in indoor environments. Epidemiologic studies of underground miners with exposure to radon and experimental evidence have established that radon causes lung cancer. The finding that this naturally occurring carcinogen is present in the air of homes and other buildings has raised concern about the lung cancer risk to the general population from radon. I review current approaches for assessing the risk of indoor radon, emphasizing the extrapolation of the risks for miners to the general population. Although uncertainties are inherent in this risk assessment, the present evidence warrants identifying homes that have unacceptably high concentrations.

(Samet JM: Indoor radon and lung cancer—Estimating the risks. West J Med 1992 Jan; 156:25-29)

Radon, a naturally occurring radioactive gas in the decay series of uranium 238 (Figure 1), is ubiquitous in indoor environments.[1] Radon is also present in the air of underground mines where it is released from ore or transported into the mine in water. More than 100 years ago, miners of metal ore in Schneeberg, Germany, were found to be at risk for lung cancer.[2] Early in the 20th century, high levels of radon were measured in the Schneeberg mines and in nearby mines in Jáchymov (Joachimstal), Czechoslovakia, where high lung cancer rates were also noted; the radon was hypothesized to be a possible cause of the high rates of lung cancer in the miners. Subsequent epidemiologic studies of other populations of underground miners have provided strong and consistent evidence that radon causes lung cancer through damage to target cells in the tracheobronchial epithelium. The damage is inflicted by the α-particles released by short-lived radon progeny (Figure 1).[3]

The presence of radon in indoor air was documented as early as the 1950s.[4] Beginning in the 1970s, research was initiated to address sources of indoor radon, determinants of concentration, health effects, and approaches to mitigation. In the United States, the problem of indoor radon received widespread publicity and intensified investigation after a widely publicized incident in 1984. During routine monitoring at a Pennsylvania nuclear power plant, a worker was found to be contaminated with radioactivity. A high concentration of radon in his home was subsequently identified as responsible for the contamination. High levels of radon have now been documented in homes in the region of the Northeast where this worker lived and in many other locations throughout the United States.

In the US, concentrations of radon in homes are generally expressed in units of picocuries (pCi) per liter. For historic reasons, the concentration of radon progeny in mines has been expressed as Working Levels (WL), a unit based on the α-particle energy of the mixture of radon progeny.[5] Under the conditions of radioactive equilibrium between radon and its progeny, assumed to typically prevail in a home, 1 pCi per liter is equivalent to about 0.005 WL. Exposure to radon progeny is measured as Working Level Months (WLM), with exposure at 1 WL for 170 hours, the approximate number of hours worked monthly, yielding 1 WLM. Because most persons spend more than 170 hours per month at home, a concentration of 1 WL in a home typically yields an exposure greater than 1 WLM monthly. In other countries, these units of concentration and exposure have been replaced by the Système International (SI) units. In SI units, the concentration of radon in air is expressed as becquerels per cubic meter (Bq per m^3), where 37 Bq per m^3 equals 1 pCi per liter. Cumulative exposure in SI units is expressed in joule-hours per cubic meter (Jh per m^3), and 1 WLM is 3.5×10^{-3} Jh per m^3.

Measurements made in the surveys of states conducted by the US Environmental Protection Agency (EPA) and in other studies have shown that the distribution of radon concentrations indoors is approximately log normal, with a mean concentration of about 1 to 1.5 pCi per liter in living areas (Figure 2).[6] Many homes have concentrations well above the average, even exceeding occupational standards set for underground mines. Two features of this distribution merit consideration in judging the public health risk posed by radon. First, the population's average exposure largely reflects the contribution of time spent in homes with lower concentrations; thus, the burden of lung cancer attributable to indoor radon predominantly results from lower levels of exposure.[7] Second, the number of homes considered as possibly having unacceptable concentrations varies markedly with the selected limit for acceptability. As the value for the limit drops below 4 pCi per liter, the number of homes exceeding the acceptable concentration increases rapidly.

The development of national policy for indoor radon, or other indoor pollutants of health concern, should be based on an understanding of the population's pattern of exposure, the risks of disease associated with exposure, the capability of accurately measuring exposure, the availability of effective techniques for preventing and mitigating exposure, and the costs of managing the risks of exposure. The technique of quantitative risk assessment has an increasingly prominent

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ABBREVIATIONS USED IN TEXT

BEIR IV = [Committee on] Biological Effects of Ionizing Radiation IV
EPA = Environmental Protection Agency
SI = Système International
WL = Working Level
WLM = Working Level Months

role in gauging the extent of a hazard as a basis for policy development.[8] In the United States, although the EPA does not have statutory authority to regulate directly the concentrations of radon in the air of homes, it has, through its Radon Program, taken the lead in developing policy. The EPA promulgates action guidelines for acceptable concentrations indoors and also advises concerning techniques for measuring, preventing, and mitigating high concentrations of indoor radon. The pamphlet, "A Citizen's Guide to Radon," sets out the EPA's approach to measurement and control and provides action guidelines for concentrations requiring a specific response.[9] The agency encourages testing nearly all homes as a basis for controlling indoor radon. The "Citizen's Guide" is currently undergoing revision.

Assessing the Risks of Indoor Radon

Three distinct approaches merit consideration as being potentially informative for estimating the risks of indoor radon:

- A deterministic model is used that directly links concentration to carcinogenic response, based on a full understanding of the biologic basis of carcinogenesis by radon progeny;
- Risk estimates are developed from epidemiologic investigation of indoor radon and lung cancer; and
- Risks observed in underground miners with exposure to radon are extrapolated to the general population.

The first approach, using a comprehensive biologic model, cannot yet be implemented with sufficient confidence in the results because of gaps in our understanding of carcinogenesis by radon progeny. With regard to the second approach, many epidemiologic studies using the case-control design are presently being conducted to estimate directly the lung cancer risks of indoor radon.[10] Because most of these studies are not yet completed, the third option, extrapolating from the studies of miners to the general population, has served as the principal approach for assessing the risk of indoor radon exposure.[3,11]

Model-Based Approaches

Model-based approaches have been applied in the past to estimate the risks of lung cancer associated with exposure to radon progeny. Using mathematic representations of the respiratory tract, the dose of α-particle energy delivered to target cells in the respiratory tract can be estimated.[3] By combining the dose estimates with risk coefficients describing the increased risk per unit of a biologically effective dose, risk projections can be made. This approach is subject to many uncertainties, and it has been rejected by recent expert panels in favor of risk estimation using the data from studies of miners.[3] As the understanding of carcinogenesis by radon progeny advances, it may become possible to develop more biologically accurate models that offer more confident risk projections. Research supported by the US Department of Energy and other agencies has this goal.

Epidemiologic Approach

After the problem of indoor radon was recognized, lung cancer mortality or incidence rates for geographic areas,

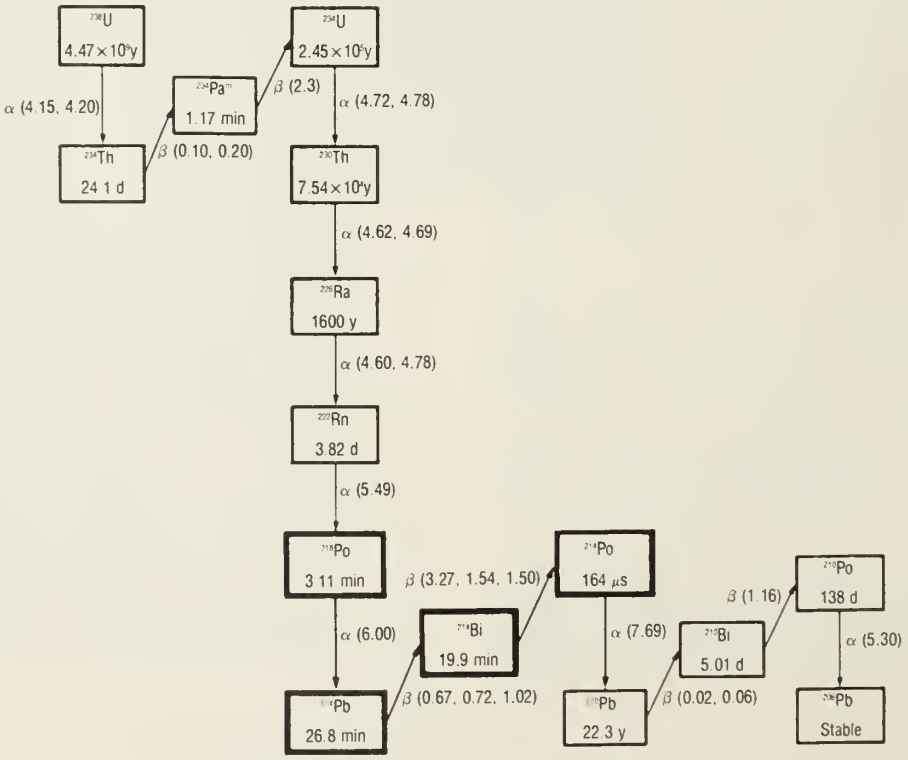

Figure 1.—The principal decay pathway is shown for uranium 238. Short-lived radon progeny are indicated by bold outline (modified from Figure 1-2 in Nero[1]; reprinted with permission).

such as counties, were correlated with estimated radon concentrations for these units. This type of epidemiologic investigation, termed an "ecologic" study, has well-described limitations.[12] The results of ecologic studies are potentially limited by uncertainties in estimating exposure, an inadequate control of factors confounding and modifying the relation of radon with lung cancer such as cigarette smoking, and biologically inappropriate assumptions that may be implicit in the statistical methods used to analyze the data.[13] Thus, although many ecologic studies have shown a positive correlation of estimated indoor radon concentration and lung cancer rates, the results are not informative for estimating the risk of lung cancer associated with indoor radon concentrations. Several studies showing either a lack of association of radon concentration with lung cancer rates, or even a negative association, have received widespread media attention.[14] The incongruity of these findings with the assumed carcinogenicity of indoor radon has been emphasized by critics of programs to control radon,[15] although the negative studies share the limitations of the positive studies. Moreover, the findings of these purportedly negative ecologic studies are inconsistent with the strong evidence from epidemiologic studies of miners and from studies of animals and with present concepts of carcinogenesis by α-particles.

The risks of indoor radon are being assessed in epidemiologic studies using the case-control design; estimated exposures of lung cancer cases to radon are compared with exposures of control subjects not having lung cancer.[16] Case-control studies of indoor radon and lung cancer have already been reported, some showing no association of radon exposure with lung cancer risk, and others showing exposure-response relations compatible with those observed in the studies of underground miners.[11,17,18] Worldwide, 15 or more case-control studies are in progress or are planned.[10]

Case-control studies of any disease have well-characterized limitations that reflect the difficulty of obtaining accurate information on exposures of concern, selecting the control series, correctly classifying cases, and controlling for relevant confounding and modifying factors. Estimating exposure is particularly problematic for case-control studies of indoor radon and lung cancer. Exposure occurs throughout the lifetime of a subject, and most persons have lived in many dwellings during their lives. To estimate exposures in the

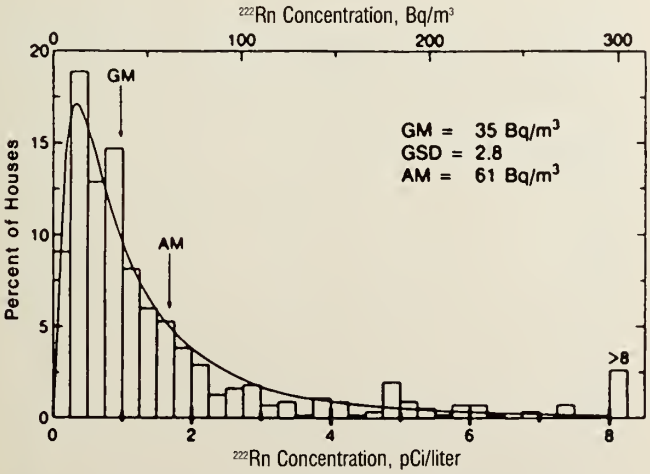

Figure 2.—The probability distribution of radon 222 in US homes is given, based on 19 data sets that include 552 homes (from Nero[1]). AM = arithmetic mean, GM = geometric mean, GSD = geometric standard deviation

TABLE 1.—*Sample Size Requirements in a Lung Cancer Case-Control Study to Detect a Trend in Risk With Radon Exposure; Effects of Radon Measurement Error and Population Mobility**

Measurement Error, %	Mobility Pattern: 1 Residence, 60 yrs	Mobility Pattern: 6 residences, 10 yrs each
None	251	1,446
30	288	2,303
50	365	4,059
100	973	18,032
150	4,186	91,875
200	29,542	674,540

*Number of cases is shown in a hypothetical study with 2 controls per case designed to reject the null hypothesis of no trend with exposure, assuming the true increment is 1.5% per Working Level Month (from Lubin et al [Table 5][16]).

context of a case-control study, a subject's current and former residences are identified, and radon concentrations are measured; it is assumed that current concentrations reflect those during the period a person resided in the residence. This retrospective estimation is subject to diverse sources of uncertainty, and feasibility may be compromised by the difficulty of identifying and gaining access to all previous residences. Moreover, the measuring devices themselves have inherent error.

Lubin and co-workers assessed sample size needs for case-control studies of radon.[16] Their analysis showed that large sample sizes are needed to have adequate statistical power for addressing the scientific hypotheses inherent in the information needs of policymakers (Table 1). For example, Table 1 shows the number of cases needed to identify a statistically significant trend of lung cancer risk with radon, comparable to the value observed in the studies of miners, as the degree of error in measuring radon and population mobility increases. Population mobility reduces the variation of exposures and thereby necessitates larger sample sizes. Similarly, increasing measurement error also increases sample size needs. Because of the complexity of estimating lifetime exposure to radon, it is likely that the measurement error is at least 50% or even higher.[16] These sample size calculations suggest that individual studies will not provide sufficiently informative answers to guide the evolution of policy on indoor radon.

Because of the limited informativeness of the individual studies, the pooling of results using meta-analysis techniques has been proposed.[10] An international effort is in progress to link the results of the case-control studies now under way.

Estimating Risk Using the Studies of Underground Miners

The risk of lung cancer associated with exposure to radon decay products has been investigated in about 20 different populations of underground miners (Table 2). Almost all of these studies show a significant excess occurrence of lung cancer in comparison with the expected number of cases. About half of the studies include data on the exposures of individual miners to radon progeny; this detailed information is needed to estimate quantitatively the lung cancer risk associated with radon exposure.

To describe the increasing frequency of lung cancer with increasing exposure, statistical approaches are used to derive risk coefficients; these coefficients describe the increment in lung cancer risk per unit exposure to radon. The range of

TABLE 2.—*Populations of Underground Miners Included in Epidemiologic Investigations of Lung Cancer**

Substance Mined	*Location of Study*
Uranium	US: Colorado Plateau, New Mexico; Czechoslovakia; Canada: Ontario, Beaverlodge, Port Radium; Uranium Hill, Australia
Iron	Sweden: Kiruna, Grangesberg, Malmberget, Northern Sweden; England; France
Tin	Cornwall, England; Yunnan Province, People's Republic of China
Magnetite	Norway
Fluorspar	Newfoundland, Canada
Zinc-lead	Hammar, Sweden
Niobium	Norway

*From Samet [Table 2].[11]

coefficients characterizing the rise of excess relative risk with exposure is remarkably narrow among the reported investigations, spanning from 0.5 to 3.0 per 100 WLM.[11] A coefficient of 1 per 100 WLM (1% per WLM) implies that the lung cancer risk is doubled by a cumulative exposure of 100 WLM.

To estimate the risk of lung cancer associated with indoor radon, a risk coefficient derived from the studies of miners is used in a mathematic model to project the occurrence of cases of lung cancer caused by exposure. Such risk-projection models require explicit assumptions concerning the temporal expression of lung cancer risk after exposure and the effects of such potentially important factors as age at exposure, age at risk, and cigarette smoking. The two most widely applied risk-projection models are the relative risk and the attributable risk models; the relative risk model assumes that the background rate of lung cancer, which incorporates the effect of cigarette smoking, is multiplied by the risk from radon, whereas the attributable risk model assumes that the excess risk is additive to the background rate. Models incorporating time dependence of risk have also been described.

Diverse risk-projection models have been developed.[3,11] Because of differing underlying assumptions, the risk projections from these models may differ substantially.[11,19] For example, three models were published during the 1980s by agencies concerned with radiation risks, including the National Council for Radiation Protection and Measurements,[20] the International Commission on Radiological Protection,[21] and the National Research Council.[3] Projections of the incremental risk associated with exposure to 1 WLM are provided in Table 3. The percentages in the table describe the increment in risk from the radon progeny beyond the background risk for lung cancer. For example, the model of the National Research Council's Committee on the Biological Effects of Ionizing Radiation IV (BEIR IV) projects that exposure to 1 WLM at age 15 increases the lung cancer risk at age 35 years by 1.5% of the background risk of that age. A wide range of estimated risk is evident among the projections of the three models.

Extrapolation of Risk

In extrapolating risk from the studies of miners to the indoor environment, assumptions must be made concerning the relations between exposure to radon progeny and the dose of α-energy delivered to the respiratory tract in the two environments and other factors potentially modifying the carcinogenicity of radon progeny (Figure 3). Exposure-dose relations in the respiratory tract can be assessed using dosimetric models, which incorporate physical characteristics of the inhaled air and biologic features of the respiratory tract. In a recent report, another committee of the National Research Council assessed the comparative exposure-dose relations of radon progeny in the indoor and mining environments.[22] The committee's analysis suggested that exposure to radon progeny in the indoor environment was somewhat less potent in causing cancer than exposure in the mining environment. The committee's review identified other sources of uncertainty in using the data from underground miners, including a lack of information on exposure during infancy and childhood, the limitation of the studies of miners to men, little information on the combined effects of smoking and radon exposure, and incomplete information on the lifetime expression of the excess incidence of lung cancer associated with radon progeny exposure.

Although subject to uncertainties, the use of epidemiologic data from miners to estimate lung cancer risks from indoor radon indicates that indoor radon poses a substantial public health problem. Using the risk model developed by the BEIR IV Alpha Committee, Lubin and Boice estimated that about 13,300 lung cancer deaths annually are attributable to indoor radon exposure.[7] The EPA estimates radon risks by combining the BEIR IV model with the model developed by the International Commission on Radiological Protection and has attributed about 20,000 lung cancer deaths annually to indoor radon.[23] The new findings of the National Research Council's committee on comparative exposure-dose relations in homes and mines suggest that these estimates should be reduced by about 25%.[22] The EPA is currently revising its estimates.

Summary

Radon, a well-documented industrial cause of lung cancer in underground miners, is a ubiquitous indoor pollutant. Many homes have high radon concentrations, even in excess of the levels now permitted in underground mines. Extensive epidemiologic studies of underground miners, in addition to complementary investigations of animals, unquestionably establish the carcinogenicity of radon and provide a basis for estimating the risks of indoor radon. The resulting risk projections, about 10,000 to 20,000 cases of lung cancer annu-

TABLE 3.—*Increment in Lung Cancer Risk for 1 WLM at Age 15 or 35 Years Projected by 3 Models**

Increment (%) at Attained Age (yr)	*Model*			
	NCRPM†			
	Male	*Female*	*ICRP‡*	*BEIR IV§*
	Exposure at age 15 yr			
35	0	0	1.9	1.5
50	0.3	0.7	1.9	1.5
65	0.05	0.2	1.9	0.5
85	0.02	0.1	1.9	0.5
	Exposure at age 35 yr			
50	0.6	1.4	0.6	3.0
65	0.1	0.4	0.6	0.5
85	0.05	0.2	0.6	0.5

*From Samet (Table 8).[11]
†From the National Council on Radiation Protection and Measurements (NCRPM).[20]
‡From the International Commission on Radiological Protection (ICRP).[21]
§From the Committee on the Biological Effects of Ionizing Radiation IV Alpha (BEIR IV).[3]

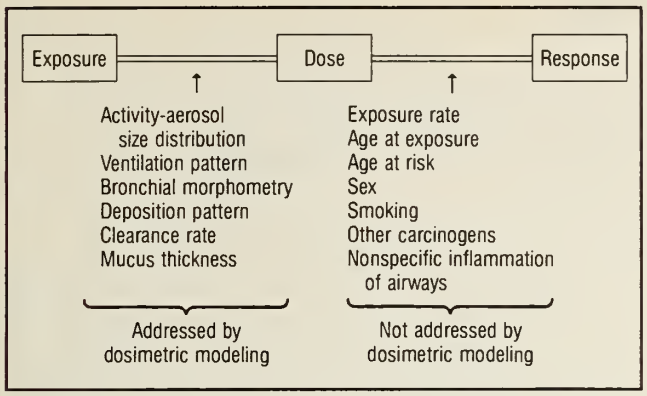

Figure 3.—Sources of uncertainty are shown in extrapolating radon risks from studies of miners to the general population exposed indoors (from the National Research Council[22]).

ally in the United States, indicate the significant public health problem posed by indoor radon.

Despite the extent of the evidence available, the risk posed by indoor radon has been questioned. Uncertainties in extrapolating data from miners to the general population and a failure to quickly confirm the hazard through epidemiologic studies are the most often cited arguments (Health Physics Society Newsletter, January 1991).[15] Ecologic studies, however, have substantial methodologic limitations for addressing indoor radon exposure, and even case-control studies may not be sufficient until their data are pooled. In the meantime, dosimetric analyses, as recently reported by the National Research Council's Committee, indicate that indoor radon delivers only a moderately lower dose of α-energy to the lung in comparison with exposure in mines. Thus, the present evidence warrants the conclusion that indoor radon should be considered a human carcinogen and justifies efforts to identify homes with unacceptably high concentrations. Research in progress can be expected to reduce uncertainties and provide more precise characterization of the risk of indoor radon.

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Articles

Seroepidemiology of Viral Infections Among Intravenous Drug Users in Northern California

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Intravenous drug users are frequently exposed to parenterally transmitted viral infections, and these infections can spread to the general population through sexual activity. We investigated the prevalence of serologic markers for human immunodeficiency virus type 1 (HIV-1), human T-cell lymphotropic virus type I/II (HTLV-I/II), hepatitis B virus (HBV), and hepatitis C virus (HCV) in intravenous drug users and their sexual contacts. Of 585 drug users from northern California tested for these serologic markers, 72% were reactive for the antibody to HCV, 71% for the antibody to hepatitis B core antigen, 12% for HTLV-I/II antibodies, and 1% for the HIV-1 antibody. The prevalence of serologic markers for these four viruses correlated with the duration of intravenous drug use, the ethnic group, and the drug of choice. More than 85% of subjects infected with either HCV or HBV were coinfected with the other virus. All persons reactive to HTLV-I/II antibodies had antibodies for either HBV or HCV. Of 81 sexual contacts tested, 17% had evidence of HBV infection while only 6% were reactive for HTLV-I/II antibodies and 4% for the antibody to HCV. None of this group was infected with HIV-1.

We conclude that HTLV-I/II and HCV are inefficiently transmitted to sexual contacts while HBV is spread more readily. Programs designed to discourage the sharing of drug paraphernalia, such as needle and syringe exchanges, should decrease the risk of parenterally spread viral infections in intravenous drug users and thus slow the spread of these infections to the general population.

(Zeldis JB, Jain S, Kuramoto IK, et al: Seroepidemiology of viral infections among intravenous drug users in northern California. West J Med 1992 Jan; 156:30-35)

Intravenous (IV) drug users acquire parenterally transmitted viral agents often by sharing needles, syringes, and other paraphernalia.[1] Regional differences in the prevalence of human immunodeficiency virus type 1 (HIV-1) infection in IV drug users reflect the date of introduction of the infection and the manner in which drug paraphernalia are shared.[2-10] In the United States, regional variation of the prevalence of antibody to human T-cell lymphotropic virus type I and II (HTLV-I/II) has been observed.[11-13] Horizontal, vertical, and blood-borne vectors of the transmission of HTLV-I/II have been reported.[10-17] Both hepatitis B and C viruses are transmitted parenterally.[18,19] Thus, IV drug users are at risk for acquiring all four infections.

We have studied the demographics and sharing patterns of IV drug users in the Sacramento, California, area and have determined the prevalence of several parenterally transmitted viral infections in these persons and some of their drug-free sexual contacts who participate in drug treatment programs. These infections are hepatitis B virus (HBV), hepatitis C virus (HCV), HTLV-I/II, and HIV-1. The duration of IV drug use and the relative ease by which these agents are transmitted sexually and parenterally determine the prevalence of these infections in the different drug-injecting groups in northern California.

Subjects and Methods

Subjects

The target population consisted of persons enrolled in the two major drug treatment programs (outpatient methadone detoxification and maintenance program and residential 21-day detoxification and long-term drug-free program) in Sacramento, from August 1987 to June 1989. These persons were offered education regarding the acquired immunodeficiency syndrome (AIDS) and testing for HIV-1 antibody at no cost. Fliers regarding the study were posted, and all staff members were informed about the study. The University of California, Davis, has an ongoing project to assess the effect of intensive, repeated AIDS prevention education on the spread of HIV-1 among IV drug users and their sexual partners. Persons who identified themselves as either an IV drug user or a sexual partner of one and who volunteered to participate were admitted into the program.[20] No tally was made of those persons who declined, and no attempt was made to discover their reasons for nonparticipation. To be admitted into the treatment programs, these persons acknowledged having self-administered illicit parenteral drugs at least once. Of the IV drug users studied, 97% were habitual users of illicit intravenous drugs. Because the remaining 3% who do not habitually use drugs did not affect our conclusions, we have included them in our analysis.

The study has five components of interactions with drug users: pretest counseling, behavioral data collection, serologic testing, posttest counseling at the time the results are released, and retesting and counseling four or more months after the first visit. During the pretest counseling session, each person was informed about the risk of infection, HIV transmission, methods of preventing transmission, and the HIV antibody blood test. Along with demographic informa-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
anti-HBc = antibody to hepatitis B core antigen
anti-HBs = antibody to hepatitis B surface antigen
EIA = enzyme immunoassay
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HCV = hepatitis C virus
HIV-1 = human immunodeficiency virus type 1
HTLV-I/II = human T-cell lymphotropic virus type I and II
IV = intravenous

tion, confidential behavioral data were collected on drug use and paraphernalia sharing habits, disinfection techniques, and sexual practices during a one-on-one interview by research staff using a standardized questionnaire.

After informed consent was obtained, blood was drawn for testing from 585 IV drug users and 81 persons who denied personal IV drug use but who were sexual partners of drug injectors either occasionally (11 persons) or for prolonged periods (70 persons). These blood specimens were subsequently tested for serologic markers for HBV, HCV, HTLV-I/II, and HIV-1. Non–drug-using sexual partners who participated in the project came to the program either with their partners or by themselves as they perceived their own risk for HIV infection. All of the participants denied homosexual contacts.

Serologic Assays

Serum specimens were obtained from the 585 IV drug users and 81 sexual partners of IV drug users. All serum was frozen immediately after separation from the cellular elements of blood and stored below −20°C before analysis. These specimens were tested for hepatitis B surface antigen (HBsAg, Auszyme, Abbott Laboratories, Inc, North Chicago, Ill) and for antibodies to the hepatitis B core antigen (anti-HBc, Corzyme, and anti-HBs, Ausab, Abbott Laboratories), hepatitis C (anti-HCV, Ortho HCV ELISA Test System, Ortho Diagnostic Systems, Inc, Raritan, NJ), HIV-1 (anti–HIV-1, enzyme immunoassay [EIA] by Genetic Systems, Seattle, Washington, and Western blot by University of California, Davis, Virus Laboratory done according to Centers for Disease Control criteria), and HTLV-I/II (anti–HTLV-I/II, HTLV-I EIA Diagnostic Kit, Abbott Laboratories, and confirmed by immunofluorescent assay[21] performed by the California Department of Health Services Viral and Rickettsial Diseases Laboratory using in-house reagents).*

Statistical Methods

The combined effects of age, number of years of IV drug use, ethnic group, drug of choice, and sex were studied with multiple logistic regression. Only effects significant at $P < .05$ are reported. The data were maintained on a Paradox data base and analyzed with the Statistical Analysis System[22] software library and the Biomedical Computer Programs logistic regression program.[23]

Results

Intravenous Drug Users

A total of 585 heterosexual IV drug users were evaluated for four parenterally acquired viral infections (Table 1). The average age of this group was 33 years. Although most (60%) were men, there was no difference in the prevalence of serologic markers by sex. Most drug injectors (74%) were white. Most (74%) had at least a high school education, but 72% were unemployed. Heroin was used by 76%. The members of this group had lived in the Sacramento metropolitan area for an average of 11 years. Nearly all (94%) shared their paraphernalia at least occasionally, usually within their own ethnic group.

The most prevalent serologic markers among IV drug users were anti-HCV (421 of 585 [72%]) and anti-HBc (417 of 585 [71%]; Figure 1). The univariate analyses are shown in Table 2, and the logistic regressions of the same data are shown in Table 3. For the categoric factors, the logistic regression results are displayed as adjusted odds ratios for each category versus a baseline group. For years of IV drug use, the relative odds for each additional five years are given. Also given are the z statistics (coefficient or standard error) produced by the logistic regression program. The logistic results generally confirm the univariate analyses.

Of the 585 IV drug users, 70 (12%) were reactive to HTLV-I/II antibodies, with a greater prevalence of this marker in African Americans and Hispanics than in whites. The frequency of anti-HBs was significantly higher in Hispanics than in either whites or African Americans. As of June 1989, only 8 (1.4%) of the IV drug users were reactive to the HIV-1 antibody.

The presence of each viral marker except HBsAg corre-

TABLE 1.—*Demographic Data on Intravenous (IV) Drug Users in Sacramento, California (n=585)**

Demographics	*Patients, No. (%)*
Sex	
Men	344 (59)
Women	241 (41)
Ethnic origin	
White	430 (74)
Hispanic	100 (17)
African American	30 (5)
Asian	9 (1.5)
Native American	7 (1)
Other	9 (1.5)
Education, grade	
<12	152 (26)
12	262 (45)
>12	171 (29)
Drug history	
IV drug of choice	
Heroin	446 (76)
Amphetamines	88 (15)
Cocaine	41 (7)
Other	10 (2)
Sharing of paraphernalia	
Never	33 (6)
Sometimes	276 (47)
Often	68 (12)
Usually	79 (14)
Always	116 (20)
Not known	13 (2)
Disinfection	
Never	168 (29)
Sometimes	137 (23)
Often	29 (5)
Usually	89 (15)
Always	122 (21)
Not known	40 (7)

*Average duration of drug use, 15 years; average duration of IV drug use, 11 years.

*Abbott Laboratories, Inc, and Ortho Diagnostic Systems, Inc, donated the immunoassays.

lated with the duration of intravenous drug use (Figure 2). This is most apparent in the 188 IV drug users with less than five years of drug use who lack the HIV-1 antibody entirely. They began the parenteral use of illicit substances after publicity about the possibility of contracting AIDS through needle sharing was widespread. The 336 IV drug users who had serologic markers for both HBV and HCV (57% of participants) averaged 13 years of injecting drugs compared with an average of only 4.6 years for the 83 (14%) who lacked markers for both. Every five years the adjusted odds of acquiring a viral infection increased by 100% based on anti-HCV reactivity, by 50% based on anti–HTLV-I/II reactivity, by 80% with anti-HBs reactivity, and by 40% with anti-HBc reactivity (Table 3). The current practice of needle and syringe disinfection did not significantly affect the distribution of viral markers. This may be due to the recent (within the past three years) introduction of disinfection practices in this population. We are continuing to study this population for evidence of the effectiveness of disinfection in preventing the spread of these diseases.

The years of IV drug use correlated more strongly with the acquisition of serologic markers for HTLV-I/II, HCV, and HBV than did the age of the user. The odds ratios and z statistics for the risk of each additional five years of age are all lower than the corresponding statistics for years of IV drug use. Age correlates less closely because persons in a particular age group differ in their drug use. For example, people older than 50 years had used drugs for 2 to 52 years, and most people younger than 20 years had used drugs for more than 5 years. Intravenous heroin users had a higher

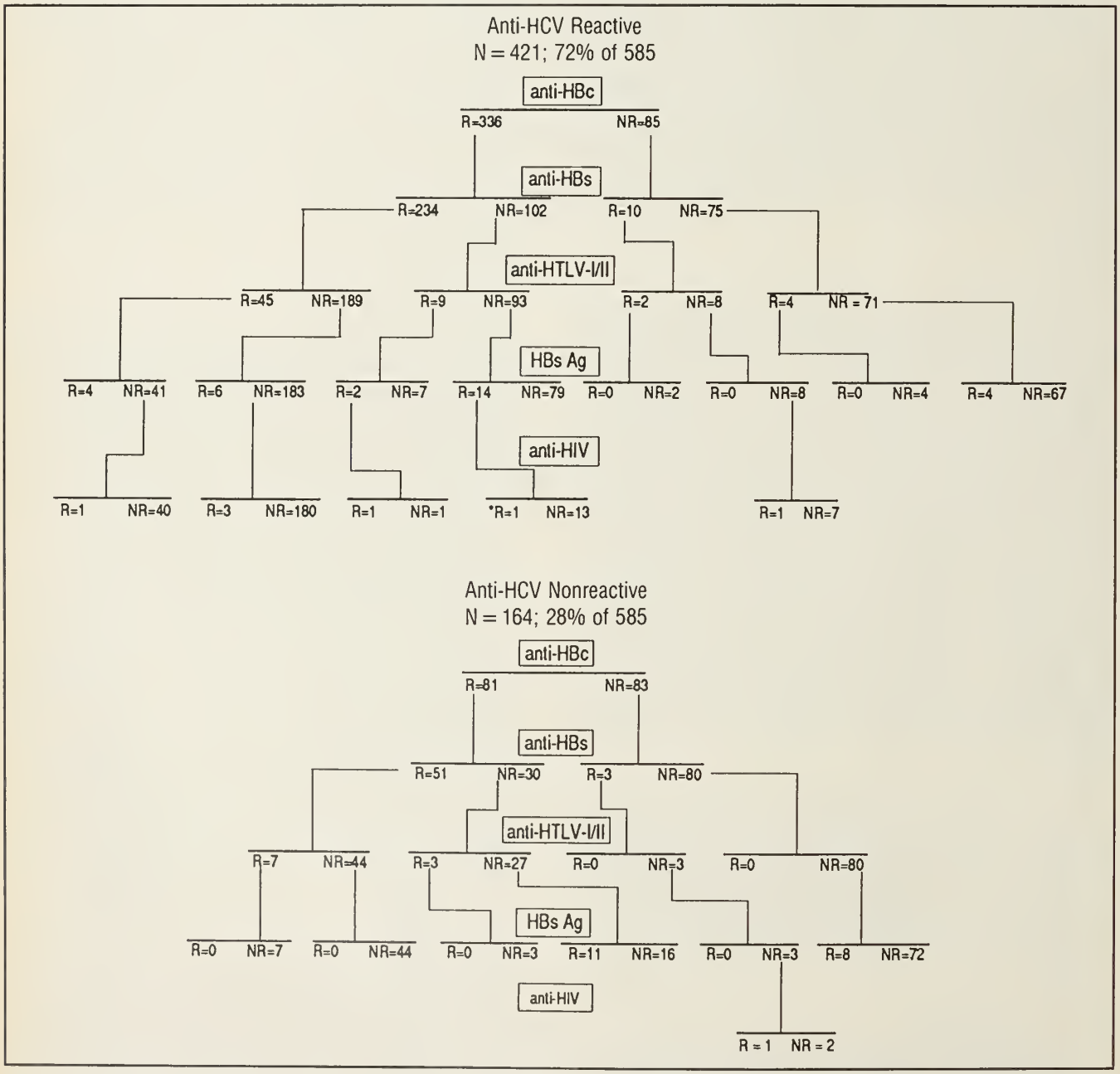

Figure 1.—The schema shows the prevalence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV), hepatitis B core [antigen] (anti-HBc), HBsAg (anti-HBs), human immunodeficiency virus (anti-HIV), and human T-lymphotropic virus types I and II (anti-HTLV-I/II) in 585 intravenous drug users, initially stratified by anti-HCV reactivity. NR = nonreactive, R = reactive, *female

TABLE 2.—*Prevalence of Serologic Markers by Ethnic Group in Intravenous Drug Users*

Ethnic Group	*n*	*HBsAg** *No. (%)*	*Anti-HBc†* *No. (%)*	*Anti-HBs†* *No. (%)*	*Anti-HCV†* *No. (%)*	*Anti-HTLV-I/II‡* *No. (%)*	*Anti-HIV-1§* *No. (%)*
White	430	35 (8)	301 (70)	212 (49)	298 (69)	35 (8)	5 (1)
Hispanic	100	8 (8)	77 (77)	63 (63)	83 (83)	22 (22)	1 (1)
African American	30	4 (13)	22 (77)	12 (40)	23 (77)	9 (30)	2 (7)
Other‖	25	2 (8)	17 (68)	11 (44)	17 (68)	4 (16)	0 (0)
TOTAL	585	49 (8)	417 (71)	298 (51)	421 (72)	70 (12)	8 (1)
P¶		NS	NS	<.01	<.05	<.0001	NS

Anti-HBc = antibody to hepatitis B core [antigen], Anti-HBs = antibody to hepatitis B surface [antigen], Anti-HCV = antibody to hepatitis C virus, Anti-HIV-1 = antibody to human immunodeficiency virus, Anti-HLTV-I/II = antibody to human T-lymphotropic virus I and II, HBsAg = hepatitis B surface antigen

*Confirmed positive by neutralization.

†Reactive more than once on enzyme immunoassay.

‡Confirmed by indirect fluorescent antibody test except 1 white, or 34 (8%) positive, and 2 Hispanics, or 20 (20%) positive, for a total of 67 (12%).

§Confirmed positive by Western blot using Centers for Disease Control criteria for anti-HIV-1.

‖Other includes Asian Americans, Native Americans, and people whose ethnic origin could not be classified.

¶The prevalence of the serologic markers for anti-HTLV-I/II in whites is compared with that in blacks and Hispanics, and the prevalence for anti-HBs and anti-HCV in Hispanics is compared with that in whites. Comparisons in the prevalence of other serologic markers were not statistically significant (NS).

prevalence of both HBV and HCV markers than persons who used IV amphetamines, cocaine, or other substances (Figure 3). This difference is independent of years of IV drug use (Table 3), despite the observation that the duration of drug use for heroin addicts (12.6 years) was greater than that for users of either amphetamines (7.2 years) or cocaine (5.5 years).

Serologic evidence of coinfection with HBV, HCV, and HTLV-I/II was common (Figure 4). Overall, 336 IV drug users (57%) were reactive to both anti-HBc and anti-HCV; 54 (9%) showed evidence of coinfection with all three viruses (HBV, HCV, and HTLV-I/II). By far the greatest correlation is seen between HBV and HCV, where 81% of the 417 anti-HBc–reactive subjects were also reactive to anti-HCV and 80% of the 421 reactive for anti-HCV were also anti-HBc reactive. In addition, all 70 people reactive to anti–HTLV-I/II were also reactive for either anti-HBc (14%), anti-HCV (9%), or both (77%).

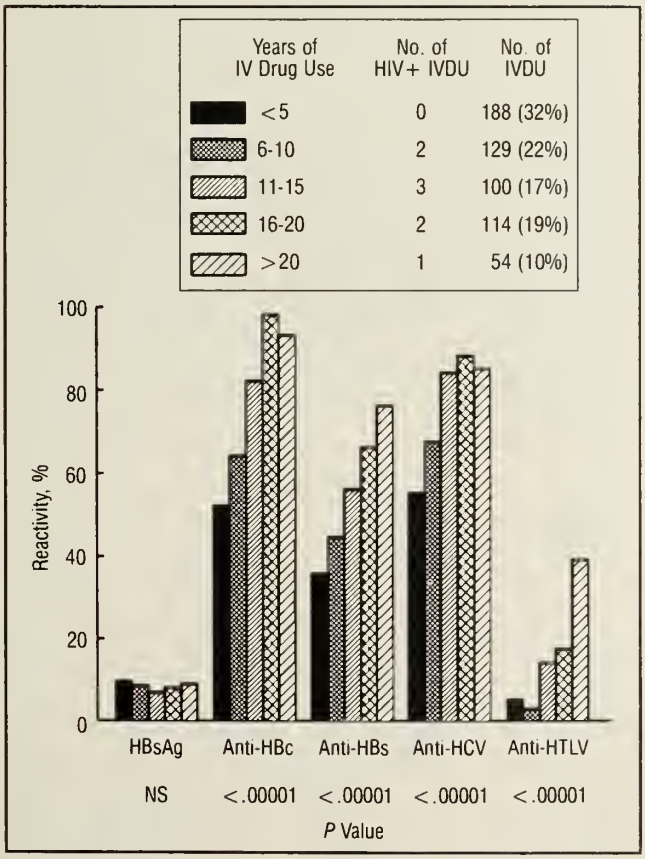

Figure 2.—Serologic markers for parenterally transmitted viral infections are correlated with the duration of intravenous (IV) drug use. Anti-HBc = antibody to hepatitis B core [antigen], Anti-HBs = antibody to hepatitis B surface [antigen] (HBsAg), Anti-HCV = antibody to hepatitis C virus, Anti-HTLV = antibody to human T-lymphotropic virus, HIV+ = human immunodeficiency virus positivity, IVDU = IV drug user, NS = not significant

All eight persons positive for the HIV-1 antibody (7 men, 1 woman) were reactive to anti-HCV. Seven of the eight had serologic evidence of current or previous HBV infection, and the eighth (who was reactive only for anti-HBs) probably had been immunized with hepatitis B virus vaccine.

Sexual Contacts

Eleven persons (6 men and 5 women) reported rare or infrequent sexual contacts with an IV drug user. Of these, three men and four women (63%) were completely seronegative. One woman was anti-HCV reactive. Three men were reactive for the HTLV-I/II antibody and one of the three was anti-HBc reactive as well.

Of the 70 persons who reported frequent sexual contact with drug injectors, none were HIV-1 infected and 53 (76%) were completely seronegative for viral infection. Three persons (4%) were reactive for anti-HCV, 13 (19%) had serologic evidence of HBV infection, and 4 (6%) were reactive to HTLV-I/II. One was coinfected with HBV and HCV, and another was reactive to both anti-HBs and anti-HBc (probably a resolved hepatitis B infection).

Discussion

The prevalence of viral infection among IV drug users in drug treatment programs during 1988 and 1989 in the Sacramento metropolitan area differed from that in other areas in California[10] and in the United States[7] in the low prevalence (1%) of antibodies to HIV-1 and the relatively low prevalence of antibodies to HTLV-I/II. These retroviruses, as well as both HBV and HCV, are assumed to be transferred readily when IV drug users share paraphernalia. Therefore, the finding that HIV-1 has not yet become well established in this community provides an opportunity to prospectively evaluate

TABLE 3.—*Odds Ratios for Risk Factors Adjusted for All Other Factors (versus Baseline Group) and z Statistics (Coefficient/Standard Error) From Logistic Regression of Seroprevalence of Virus Markers*

	Anti-HTLV I/II		Anti-HCV		Anti-HBc		Anti-HBs	
Risk Factor	*Odds Ratio*	*z*	*Odds Ratio*	*z*	*Odds Ratio*	*z*	*Odds Ratio*	*z*
Ethnic group (versus white)								
African American	8.2	3.8	3.2	2.1	1.3	0.6	0.5	−1.6
Hispanic	3.7	3.8	2.4	2.7	1.8	1.7	1.7	2.1
Other	3.1	1.8	1.0	−0.1	0.9	−0.2	0.8	−0.6
Female versus male	1.6	1.4	1.2	0.7	0.9	−0.8	0.9	−0.3
Drug of choice (versus amphetamine)								
Cocaine	7.5	1.7	1.0	0.5	1.1	0.3	1.3	0.6
Heroin	5.6	1.7	2.7	3.8	2.8	3.9	2.2	2.9
Each 5 years of intravenous drug use	2.0	6.5	1.5	4.8	1.8	6.5	1.4	4.7

Anti-HBc = antibody to hepatitis B core [antigen], Anti-HBs = antibody to hepatitis B surface [antigen], Anti-HCV = hepatitis C virus, Anti-HTLV-I/II = antibody to human T-lymphotropic virus I and II

interventional programs such as needle exchange and disinfection practices. This low prevalence presents a unique opportunity to prevent further HIV transmission such as has been observed in other similar areas with low prevalence.[24]

Serologic studies of IV drug users in the Sacramento region show a high prevalence of HBV and HCV, with a high probability of dual or multiple infections with these two viruses. Although we used a first-generation enzyme immunoassay for anti-HCV, which has a substantial number of false-positive and false-negative test results, supplemental testing suggests that more than 85% of anti-HCV EIA-reactive results from IV drug users represent actual infection (Mitchell Nellis, PhD, Ortho Diagnostics, written communication, May 1990). In fact, we may be underestimating the frequency of anti-HCV in this population because first-generation EIA identifies antibodies to only one HCV-related protein. All persons infected with HTLV-I/II had evidence of HBV or HCV infection as well. The antibody to HIV-1 was rarely found in this study population, providing an opportunity to trace its entry prospectively.

The lower prevalence of HTLV-I/II and HIV-1 than of HBV and HCV infections in this population may reflect the recent introduction of these infections into this group, fewer viral carriers, and less efficient modes of transmission.[11] The prevalence of serologic markers of HBV, HCV, and HTLV-I/II infections correlated better with the duration of IV drug use than with the age of the user, perhaps because some younger users have used illicit intravenous drugs longer than their older peers. Over the past five years of studying drug injectors, we have observed that people of all ages share their paraphernalia, but they tend to share drugs more often with persons of similar age and ethnic origin. This rate of sharing

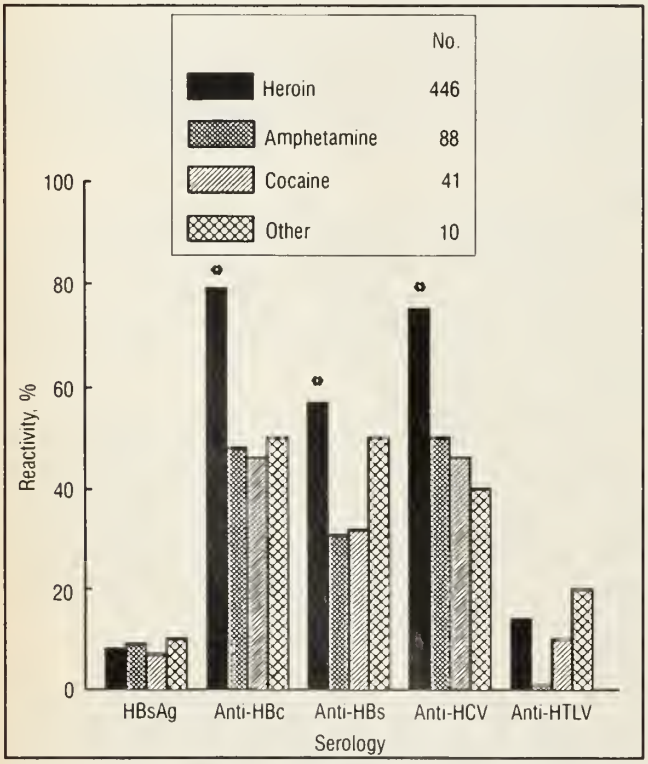

Figure 3.—Serologic markers for parenterally transmitted virus infection are correlated with the type of illicit drug used. "Other" includes intravenous barbiturates, hallucinogens, and marijuana. The asterisk (*) means that the difference in the prevalence of these markers between heroin and cocaine and amphetamine users is statistically significant ($P<.00001$). The prevalence of other markers between the drugs of choice is not statistically significant ($P>.05$). Anti-HBc = antibody to hepatitis B core [antigen], Anti-HBs = antibody to hepatitis B surface [antigen] (HBsAg), Anti-HCV = antibody to hepatitis C virus, Anti-HTLV = antibody to human T-lymphotropic virus

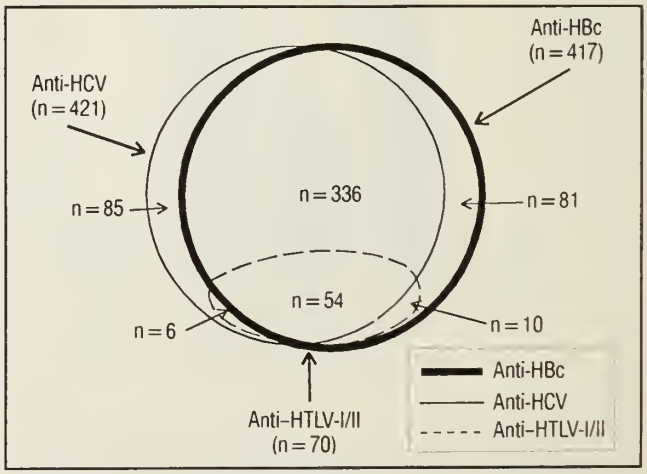

Figure 4.—A Venn diagram shows the prevalence of serologic markers for antibodies to hepatitis B virus core antigen (Anti-HBc), hepatitis C virus C100 peptide (Anti-HCV), and proteins to human T-lymphotropic virus types I and II (Anti-HTLV-I/II).

is much higher than that reported in the IV drug use study from New York City.[2,5] It also may reflect the high prevalence of HTLV-I/II infection in subjects aged 50 years or older regardless of their duration of IV drug use.

The finding that approximately 9% of subjects are HBsAg-positive regardless of the duration of IV drug use, ethnic group, and drug of choice may indicate that a small percentage of these patients have chronic HBV infection or that few are experiencing acute hepatitis B at any one time. The high frequency of HBV and HCV exposure in IV drug users supports the continued use of anti-HBc testing as a surrogate marker for hepatitis non-A, non-B infection in blood donors, even with the introduction of anti-HCV screening using an enzyme immunoassay technique.

The sexual transmission of hepatitis C occurs less frequently than that of hepatitis B, as previously reported.[25,26] Koff and co-workers reported that 23% of sexual partners of IV drug users had evidence of hepatitis B[26]; this is similar to our finding of a 17% HBV infection rate. Only 4% of sexual partners had HCV markers, however, despite a similar prevalence of anti-HBc (71%) and anti-HCV (72%) serologic markers in IV drug users.

As is true for other metropolitan areas, the ethnic composition of IV drug users in the Sacramento metropolitan area is not known. According to a 1990 report ("AIDS in Sacramento County Through 1989," by Mark D. Starr, DVM, MPVM, epidemiologist for Sacramento County Health Department), the population in Sacramento County is 71% white, 8% African American, 11% Hispanic, and 10% other. If IV drug users' ethnicity is similar to that of the general population, then in this study African Americans may be slightly underrepresented and Hispanics slightly overrepresented. Despite these drawbacks, the results from this study of persons in drug treatment programs can be compared with those of studies from other regions of the country that examined similar populations. Because we did not select our patients, other than to solicit participation of all members of drug treatment programs, we can assume that the group studied reflects the population of IV drug users in Sacramento who seek help for their addiction.

The acquisition of viruses by sexual transmission in IV drug users may differ from acquisition by parenteral transmission because of the behaviors that have been described to us by the subjects in our study. They report that although they restrict the sharing of paraphernalia to persons of similar ethnic backgrounds, many drug users interact sexually outside their ethnic and age groups. This may account for the higher prevalence of serologic markers in Hispanics and African Americans than in whites.

In most areas of the country, it is currently illegal for IV drug users to purchase or exchange needles and syringes despite information from the Netherlands and the United Kingdom[27,28] that such practices do not encourage IV drug use, decrease the sharing of paraphernalia, and decrease risk-taking activities during IV drug use. In many states (including California) where possessing needles and syringes without a prescription is a felony offense and is a frequent reason for the arrest of IV drug users, most avoid carrying their own equipment. As a consequence, 94% of these persons share needles and syringes. Our finding of an increased accrual of serologic markers for each parenterally transmitted infection with the duration of IV drug use implies that, if they would stop using drugs intravenously or sharing personal paraphernalia, the spread of many infections should decline.

One of the major goals of the University of California's AIDS Task Force is to decrease the spread of HIV and other parenterally transmitted infections by IV drug use. The prevalence data obtained in this study will serve as a basis for determining whether future interventions prevent or retard the spread of various parenterally transmitted infections.

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Articles

Primary Care Physicians' Refusal to Care for Patients Infected With the Human Immunodeficiency Virus

CHARLES E. LEWIS, MD, *Los Angeles, and* KATHLEEN MONTGOMERY, PhD, *Riverside, California*

We conducted a telephone survey of a random sample of office-based primary care physicians in Los Angeles County to determine their practice experiences with patients infected with the human immunodeficiency virus (HIV). Telephone interviews included questions related to the physicians' experiences evaluating patients for HIV infection during the past 6 months and the presence of HIV-infected patients in their practices. Those without HIV-infected patients were asked if this was because they had not encountered such patients, because those patients had died, or because the physicians had chosen to refer these patients elsewhere or the patients had gone elsewhere for care. Of physicians who participated in the survey, 78% had evaluated a patient for HIV infection in the past 6 months; 34% were currently providing primary care for infected patients; and 36% had elected to refer HIV-infected patients elsewhere, or their patients had elected to find other physicians. In all, 48% of physicians in the sample had elected not to care for, or said they would not provide care for, patients with HIV infection.

Among Los Angeles County primary care physicians, 36% have refused to provide continuing care for HIV-infected patients and another 12% indicated their unwillingness to do so should such patients present themselves for care. As of 1991, the reservoir of primary care physicians in Los Angeles not yet involved with but willing to care for HIV-infected patients is relatively small (15%).

(Lewis CE, Montgomery K: Primary care physicians' refusal to care for patients infected with the human immunodeficiency virus. West J Med 1992 Jan; 156:36-38)

A decade into the human immunodeficiency virus (HIV) epidemic, an initial concern persists: How many physicians, particularly those in primary care roles, are willing to care for HIV-infected patients? The list of reasons for avoiding these patients has been well defined: concerns of other patients, fear of personal infection with HIV, discomfort in dealing with homosexual or bisexual men, lack of "good insurance," the complexity of caring for those with multiple complications, the recent debate over mandatory testing of physicians for HIV infection, and the specter of the consequences of a positive test result on a physician's career.

An alternative question is equally persistent: How many primary care physicians have seen patients infected with HIV and have chosen not to continue to provide primary care to them? Since 1984, we have conducted periodic telephone surveys of random samples of office-based primary care physicians in Los Angeles County to determine their experiences related to the acquired immunodeficiency syndrome (AIDS). Questions dealt with physicians' involvement in the workup of patients for HIV infection, whether or not they are providing primary care for patients who are infected with HIV and for persons with AIDS, and certain practices with regard to risk assessment and counseling, such as sexual history taking. Over time, our surveys have found a gradual increase in the proportion of physicians who are caring for one or more patients with HIV infection.[1]

At the end of 1990, we conducted the fourth in this series of surveys. In inquiring about physicians' experiences with HIV disease, we also asked about their referral practices with regard to HIV-infected patients.

Physicians and Methods

The American Medical Association's listing was used to identify office-based primary care physicians in Los Angeles County in family or general practice or general internal medicine. A random sample of these physicians was selected. Physicians were sent a letter explaining the nature of the survey, its confidentiality, and that they would be contacted shortly for a telephone interview by a representative of the Institute for Social Science Research at the University of California, Los Angeles.

Interviews averaged 18 minutes and were conducted in English. Interview items were taken directly from the previous three surveys. In addition, those physicians who said they did not have any HIV-infected patients in their practices were asked whether this was because they had not encountered such patients, they had seen such patients but had chosen to refer them elsewhere, the patients had elected to go elsewhere, or their HIV-infected patients had died. Physicians who had not seen an HIV-infected patient were asked whether, if such persons presented themselves, the physicians would accept them into their practices or refer them elsewhere.*

*A copy of the interview guide is available from the authors (C.E.L.).

From the Division of Preventive and Occupational Medicine, Department of Medicine, University of California, Los Angeles (Dr Lewis), and the Graduate School of Management, University of California, Riverside (Dr Montgomery).

This study was supported in part by the Southern California AIDS Education and Training Center Grant HRSA BRT 000030.

Reprint requests to Charles E. Lewis, MD, Division of Preventive and Occupational Medicine, 61-236 Center for Health Sciences, UCLA School of Medicine, 10833 Le Conte Ave, Los Angeles, CA 90024-1772.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

Results

Of the 419 physicians in the sample, a substantial proportion listed as being in office-based primary care practice were not eligible for the study. A total of 61 physicians were not in primary care; 9 had either retired or died; 41 had moved from the practice site listed and could not be located.

In all, 83 physicians actively refused to participate, and another 23 passively refused by being unavailable on as many as 10 callbacks. Thus, the overall completion rate, excluding those not eligible, was 65.8% (N = 202).

The available characteristics of responders and nonresponders were compared. The only difference noted was a lower response rate among foreign medical graduates (55%) than among American medical graduates (78%).

As in previous surveys, all physicians spent more than 20 hours per week in patient care. General internists made up 43% of the sample; the rest were in family or general practice. The median number of patients seen per week was 100. A total of 62% were in solo, fee-for-service practice; 42% accepted patients on Medi-Cal (California's Medicaid). The physicians' median year of graduation from medical school was 1971.

Figure 1 illustrates the HIV-related experiences of this sample of physicians. The data reflect experiences per 100 physicians (or percentage of the sample). Of each 100 physicians, 78 had worked up a patient for HIV infection within the past six months; 34 were providing care for one or more HIV-infected patients. Thus, less than half of those who had worked up patients for possible HIV infection were providing primary care to at least one infected patient.

Of the 44 physicians who had no HIV-infected patients, 36 were not caring for such patients because they had referred them elsewhere or the patients elected to go elsewhere for care. (We assumed that those who elected to go elsewhere for care had done so because they were encouraged to do so or were discouraged from returning.) Only 5 of 78 physicians who had worked up a patient for possible HIV infection in the past six months had not seen or identified an infected patient. Of the 27 yet to see an HIV-infected patient in their practice, 12 would refer the patient elsewhere and 15 physicians said they would accept such a patient into their practices.

The structure of the questionnaire presented an opportunity for validating the internal consistency of responses. For example, all of the physicians who are caring for HIV-infected patients had worked up patients within the past six months; none who said they had not done such workups indicated they were providing primary care to these patients.

Discussion

There have been numerous studies of the attitudes of practicing physicians, medical school faculty, and medical students with regard to their exposure to HIV-infected patients.[2-5] Several studies have asked if the student or physician believes he or she has the right to decline to care for HIV-infected patients; only a few have directly posed questions about refusing to care for these patients.

While some authors have expressed doubt about the validity of these expressions of intent with regard to practice, one study is of particular interest. In 1985, Richardson and coworkers sent questionnaires to a random sample of members of the Los Angeles County Medical Association. Of this group (N = 314), 51.5% strongly agreed with the statement, "If I diagnosed a person to have AIDS, I would refer them."[6] Five years later, our telephone survey of a random sample of all primary care physicians in Los Angeles County found that 48% had already refused or would refuse to accept HIV-infected patients into their practices.

To our knowledge, this is the first survey that has attempted to determine the extent to which primary care physicians have elected not to care for HIV-infected patients in their practices. Although we were concerned about the truthfulness of physicians' responses to this question, telephone interviewers found physicians were willing to answer, and an item-by-item analysis of responses suggests that the responses were internally consistent. We did not ask why physicians chose not to care for these patients—for economic reasons, fear of infection, possible loss of patients, or other concerns. Because the focus was on HIV-infected patients rather than AIDS patients, we presume that the severity or complexity of illness was not a major factor.

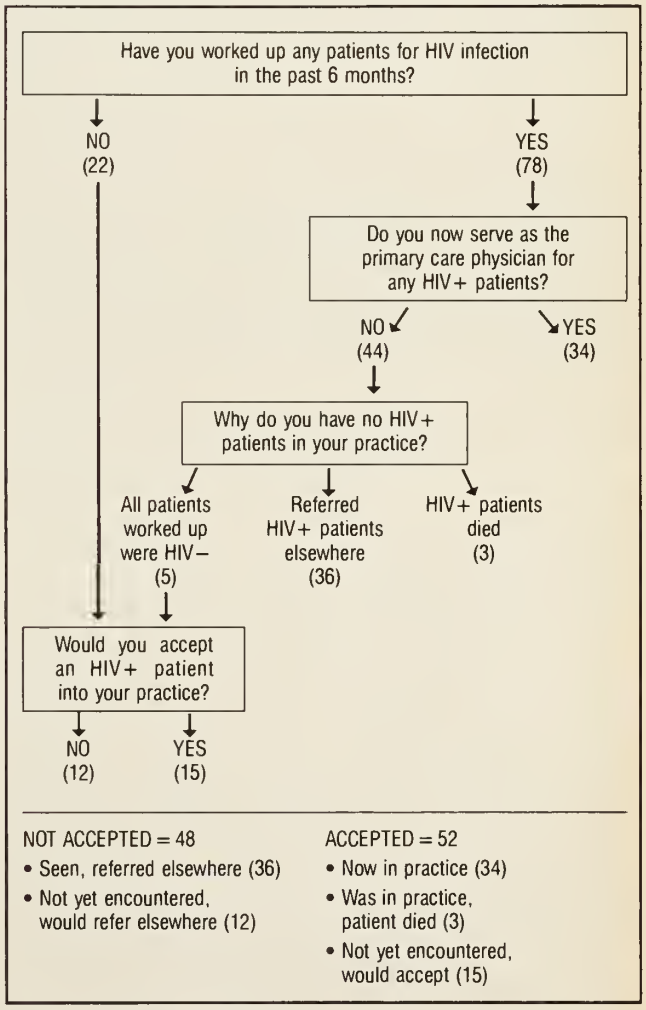

Figure 1.—Physicians' acceptance of or refusal to care for patients infected with the human immunodeficiency virus (HIV) was measured in this study as responses to several questions, as indicated. The number of responses per 100 physicians is also given.

These findings suggest that there are fewer primary care physicians in Los Angeles willing to accept new patients with HIV infections than had been expected, given past surveys that reported only the proportion who were caring for HIV-infected patients. The responses suggest that almost half of primary care physicians in Los Angeles County may have already rejected HIV-infected patients or plan not to accept them as regular patients.

Under these circumstances, a growing number of persons infected with HIV probably will need to seek care from physicians now attending these patients. According to our data, the untapped reservoir of physicians available to provide primary care to these patients is not 66% of primary care physicians (or all those who do not now have HIV-infected patients) but only 15%. Most of those not caring for HIV-infected patients have already chosen not to do so.

While these findings cannot be generalized beyond the site of the study, the county with the second largest number of AIDS cases in the United States, physicians in other communities may have made similar decisions. Future surveys of physicians' experiences with HIV disease should explore this possibility.

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Home Oxygen Therapy Under Medicare
A Primer

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Medicare recently implemented a new, strict, and complex home oxygen policy and a new oxygen prescription form. Unfortunately, the lack of instructions for the form has led to confusion, frustration, and suboptimal treatment. Long-term oxygen therapy prolongs survival, ameliorates hypoxic organ dysfunction, and improves exercise endurance. Indications for therapy include hypoxemia caused by cardiopulmonary diseases, hypoxemia that occurs with sleep or exercise, and hypoxemic organ dysfunction. Patients should be stable and have an arterial blood oxygen tension (Pa_{O_2}) of 55 mm of mercury (7.3 kPa) or less or arterial blood oxygen saturation (Sa_{O_2}) of 88% or less. There should be evidence of hypoxic organ dysfunction when the (Pa_{O_2}) is 56 to 59 mm of mercury (7.4 to 7.8 kPa) or the Sa_{O_2} is 89%. A medical review by the insurance carrier is required if oxygen is to be prescribed when hypoxemia is less severe—if the Pa_{O_2} is 60 mm of mercury (8.0 kPa) or more or if the Sa_{O_2} is 90% or more. The instructions for oxygen flow, duration, and equipment must be explicit to ensure adequate therapy. An oxygen concentrator with a small oxygen cylinder portable system fulfills most needs. Oxygen cylinders may be used at low flows for patients who require therapy only during sleep or where electrical power is unreliable. A liquid oxygen system may be prescribed for active patients. Portable equipment should be provided in addition to stationary equipment when patients have resting hypoxemia. Portable equipment alone is sufficient when there is exercise-related hypoxemia with normal oxygenation at rest. Newly developed oxygen-conserving devices may offer longer ambulatory times and possibly lower operating costs. When home oxygen therapy is started in the hospital, the Certificate of Medical Necessity should be completed and patients should be trained to use the equipment before discharge.

(Shigeoka JW, Stults BM: Home oxygen therapy under Medicare—A primer. West J Med 1992 Jan; 156:39-44)

The use of home oxygen therapy has increased dramatically because it is beneficial and the prevalence of lung disease is high.[1-3] An estimated 500,000 to 800,000 Americans use home oxygen at a cost of between $2 and $3 billion a year.[4] Alarmed by these high costs, the Health Care Financing Administration (HCFA or Medicare) in 1989 implemented a new policy to eliminate unnecessary and unreasonable prescription, simplify administration, and reduce costs.[5] This tightly regulated policy has affected services substantially because Medicare supports about 60% of the cost of home oxygen therapy.[4] The policy is complex and demanding despite the advice of health care professionals and medical equipment suppliers.[6-8] Therapy may not be supported without detailed justifications and may be suboptimal without specific instructions. That Medicare has not provided instructions for completing this form adds to the complexity and confusion. This primer presents experience dealing with Medicare-supported home oxygen therapy—that is, it is an unofficial guide. For practical reasons, we follow the outline of the HCFA Certificate of Medical Necessity for Home Oxygen Therapy (Figure 1).

Form HCFA-484 (5-90)—Attending Physician's Certification of Medical Necessity for Home Oxygen Therapy

Form HCFA-484 (5-90), available from the Medicare carrier (the local administrator, often Blue Cross/Blue Shield), serves as the prescription and justification for therapy (Figure 1). Enter information about the patient and vendor (supplier) at the top. Identify the form as "Initial" to start therapy, "Revised" to change therapy, or "Renewed" to continue therapy. Only a physician or physician's employee may complete the remainder. Medicare now forbids vendors from entering information because of concerns with inappropriate prescription.

Section 1—Pertinent Diagnoses, International Classification of Diseases, 9th Revision (ICD-9-CM), Codes, and Findings

Background

Two controlled, multicenter studies of hypoxemic patients with chronic obstructive pulmonary disease (COPD) have established the benefits of long-term, low-flow home oxygen therapy.[1,2] These include improved survival, improved neuropsychological function, and amelioration of polycythemia, pulmonary hypertension, and right-sided heart failure (cor pulmonale).[1-3] Oxygen therapy given "continuously" (more than 19 hours a day) halves the annual mortality of patients with COPD and cor pulmonale,[1] which is in excess of 65% over four years,[9] and is the only therapy known to do this. When oxygen is given for 12 to 15 hours a day, the benefit is reduced[1] and delayed.[2] Additional less convincing benefits include improved exercise endurance, reduced exercise-related dyspnea, fewer days in hospital, and the ability to resume gainful employment.[10,11]

Nearly all scientifically evaluated experience has been

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ABBREVIATIONS USED IN TEXT

CaO_2 = arterial blood oxygen content
COPD = chronic obstructive pulmonary disease
HCFA = Health Care Financing Administration
ICD-9-CM = International Classification of Diseases, 9th revision [Clinical Modification]
PaO_2 = arterial blood oxygen tension
SaO_2 = arterial blood oxygen saturation

obtained from patients with COPD who have hypoxemia at rest. The Health Care Financing Administration also accepts the treatment of hypoxemia caused by less well-studied conditions and that related to exercise or sleep.

Application

Select the pertinent diagnoses and findings. Cor pulmonale refers to jugular venous distention, liver engorgement, edema, or electrocardiographic changes of "P pulmonale" (the P wave exceeds 3 mm in leads II, III, and aVF), while polycythemia is defined as a hematocrit of 0.57 (57%) or more. When appropriate, enter the diagnosis and ICD-9-CM code for "other conditions" such as cystic fibrosis (277), pneumonia (480-486 by etiology), obstructive sleep apnea (780.53), kyphoscoliosis (737), pneumoconiosis (500-508 by etiology), or pulmonary carcinomatosis (162.8).

The Health Care Financing Administration excludes oxygen therapy for the following conditions: angina pectoris or breathlessness without hypoxemia or cor pulmonale, peripheral cyanosis due to vascular disease only, and terminal illness that does not affect the lungs.

Section 2—Dates of Last Examination and Prescription and Estimated Length of Need

Background

To eliminate unnecessary prescription, the continued medical need for oxygen therapy must be reviewed periodically. Cardiopulmonary disease should be stable before starting long-term therapy. Nearly half the Nocturnal Oxygen Therapy Trial patients who were classified as clinically stable candidates for home oxygen therapy showed sufficient improvement to stop oxygen therapy after a month of outpatient observation.[12] After an exacerbation of chronic lung disease, it is reasonable to start home oxygen therapy at

Department of Health and Human Services
Health Care Financing Administration

Form Approved
OMB No. 0938-0534

ATTENDING PHYSICIAN'S CERTIFICATION OF MEDICAL NECESSITY FOR HOME OXYGEN THERAPY *(Legible handwritten entries acceptable)*

Public reporting burden for this collection of information is estimated to average 15 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden, to HCFA, P.O. Box 26684, Baltimore, MD 21207, and to the Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, DC 20503.

Patient's Name, Address, and HIC No | Supplier's Name, Address, and Identification No

Certification ☐ Initial ☐ Revised ☐ Renewed

INFORMATION BELOW TO BE ENTERED ONLY BY PHYSICIAN OR PHYSICIAN'S EMPLOYEE

1. Pertinent Diagnoses, ICD-9-CM Codes, and Findings - CHECK ALL THAT APPLY:
   - ☐ Emphysema (492.8)
   - ☐ COPD (496)
   - ☐ Cor Pulmonale (416.9)
   - ☐ Interstitial Disease (515)
   - ☐ Other _____ Specify _____ Code
   - ☐ Chronic Obstructive Bronchitis (491.2)
   - ☐ Chronic Obstructive Asthma (493.20)
   - ☐ Congestive Heart Failure (428.0)
   - ☐ Secondary Polycythemia (289.0)
   - ☐ Hematocrit 57% or more Yes ☐ No ☐

2.A. I last examined this patient for this condition on ____/____/____ (Month Day Year)

2.B. Home oxygen prescribed ____/____/____ (Month Day Year)

2.C. Estimated length of need. ☐ 1-3 months ☐ 4-12 months ☐ Lifetime

3.A. Results of Most Recent Arterial Blood Gas and/or Oxygen Saturation Tests (Patient Breathing Room Air)

	PO2	O2 Saturation	Date
(1) At Rest			
(2) Walking			
(2) Sleeping			
(3) Exercising			
(4) Other			

3.C. Physician/Provider Performing Test(s) *(Printed/Typed Name and Address)*:

3.B. If performed under conditions other than room air, explain.

NOTE: If PO2 Level exceeds 59 mm Hg or the arterial blood saturation exceeds 89% at rest on room air, the claim will be disallowed without compelling medical evidence. Check block ☐ if you have attached a separate statement on your letterhead of additional documentation.

4. Oxygen Flow Rate ____ Liters per minute ☐ Continuous (24 hrs/day)
   ☐ Noncontinuous (Enter hrs/day): ____ Walking ____ Sleeping ____ Exercise Program ____ Other (specify) _____

5. Oxygen Equipment Prescribed If you have prescribed a particular form of delivery, check applicable block(s). Otherwise leave blank

A. Supply System
   - (1) Stationary Source: ☐ Concentrator ☐ Compressed Gas ☐ Liquid Oxygen ☐ Other
   - (2) Portable or Ambulatory Source: ☐ Liquid Oxygen ☐ Compressed Gas ☐ Other _____

B. Delivery System
   - ☐ (1) Nasal Cannula
   - ☐ (2) O2 Conserving Device
     - ☐ Pulse O2 System
     - ☐ Reservoir System
     - ☐ Other _____
   - ☐ (3) Transtracheal Catheter
   - ☐ (4) Other _____

6. If you have prescribed a portable or ambulatory system, describe activities/exercise that patient regularly pursues which require this system in the home and which cannot be met by a stationary system (e.g., amount and frequency of ambulation).

CERTIFICATION

THE PATIENT HAS APPROPRIATELY TRIED OTHER TREATMENT MEASURES WITHOUT SUCCESS. OXYGEN THERAPY AND OXYGEN EQUIPMENT AS PRESCRIBED IS MEDICALLY INDICATED AND IS REASONABLE AND NECESSARY FOR THE TREATMENT OF THIS PATIENT. THIS FORM AND ANY STATEMENT ON MY LETTERHEAD ATTACHED HERETO HAS BEEN COMPLETED BY ME, OR BY MY EMPLOYEE AND REVIEWED BY ME. THE FOREGOING INFORMATION IS TRUE, ACCURATE, AND COMPLETE, AND I UNDERSTAND THAT ANY FALSIFICATION, OMISSION, OR CONCEALMENT OF MATERIAL FACT MAY SUBJECT ME TO CIVIL OR CRIMINAL LIABILITY.

Attending Physician's Signature *(A STAMPED SIGNATURE IS NOT ACCEPTABLE)* | Date

Physician's Name, Address, Telephone No., and Identification No

Form HCFA-484 (5-90)

Figure 1.—Form HCFA-484 (5-90), the Attending Physician's Certification of Medical Necessity for Home Oxygen Therapy, is used to prescribe and justify home oxygen therapy. Except for information that identifies the patient, supplier, and type of certification, the form must be completed by the physician or physician's employee. Information is entered in several numbered areas that are described sequentially in the text.

discharge, provide optimal medical treatment, and evaluate the need to continue therapy after one to three months. If long-term therapy is required, an evaluation every six months is probably adequate.

Application

Physicians must assure the carrier that they are observing their patients closely and that the prescription is current. Our carrier accepts data from the previous month for initial certifications to start therapy, three months for revised certifications to increase or decrease therapy, and six months for renewed certifications to continue therapy even when there is a lifetime need. Our carrier rejects certificates with data that are more than six months old.

The estimated duration of need selected by the physician will affect recertification. See the discussion on "Recertification and Retesting."

Section 3A—Results of Arterial Blood Gas or Oxygen Saturation Tests

Background

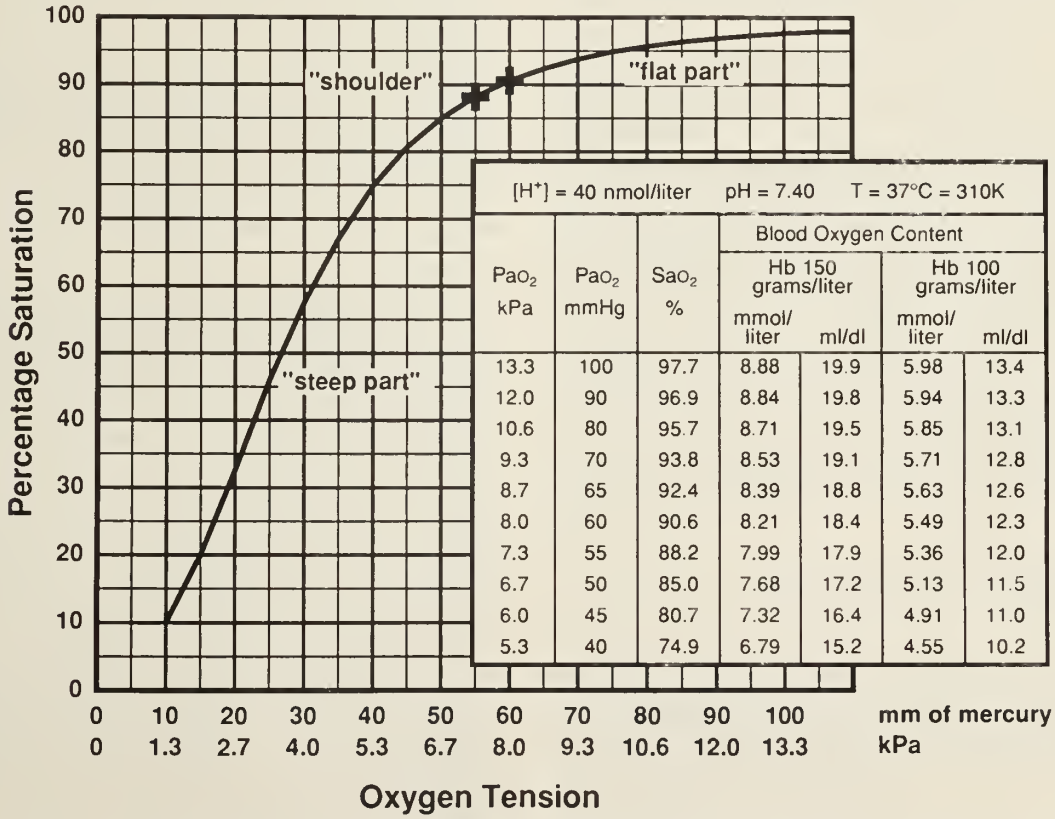
The recommendations for long-term oxygen therapy are based on pathophysiologic mechanisms, clinical observation, and technology. The hemoglobin-oxygen dissociation curve is a helpful mnemonic (Figure 2).[13] Arterial blood oxygen tensions (Pa_{O_2}) in the range of 55 to 60 mm of mercury (7.3 to 8.0 kPa) identify the shoulder of the curve that corresponds to arterial oxygen saturations (Sa_{O_2}) of 88% to 90% under normal conditions. When the Pa_{O_2} drops acutely into this range, it is common to see abnormal neuropsychological function (impaired short-term memory and judgment), physiologic responses (hyperventilation, tachycardia, and pulmonary arterial vasoconstriction), and the initiation of chronic compensatory responses (secondary polycythemia).

Below the shoulder lies the steep part of the dissociation curve where small decrements in the Pa_{O_2} produce large decrements in the Sa_{O_2} and oxygen content (Ca_{O_2}). The risk for hypoxic organ dysfunction is high when hypoxemia is this severe. When the Pa_{O_2} is 55 mm of mercury (7.3 kPa) or less, or when the Sa_{O_2} is 88% or less, Medicare supports oxygen therapy without further justification.

Cor pulmonale may develop with less severe hypoxemia in some patients either for unknown reasons ("heightened sensitivity") or in association with known aggravating conditions, such as anemia or left-sided heart failure. Medicare supports oxygen therapy when the Pa_{O_2} is in the range of 56 to 59 mm of mercury (7.4 to 7.8 kPa) or when the Sa_{O_2} is 89% if there is hypoxic organ dysfunction such as cor pulmonale, P pulmonale, polycythemia, or impaired mental function.

Above the shoulder is the flat part of the dissociation curve where a large rise in the Pa_{O_2} causes a small rise in Sa_{O_2} and Ca_{O_2} values. When the Pa_{O_2} exceeds 70 mm of mercury (Sa_{O_2} 94%), there is little gain in oxygen content. Medicare refuses to support oxygen therapy when the Pa_{O_2} is 60 mm of mercury (8.0 kPa) or more or when the Sa_{O_2} is 90% or more unless the physician provides compelling evidence that oxygen therapy has clinical benefit.

It should be noted that Medicare liberalized the Sa_{O_2}



[H+] = 40 nmol/liter pH = 7.40 T = 37°C = 310K

Pa_{O_2} kPa	Pa_{O_2} mmHg	Sa_{O_2} %	Blood Oxygen Content: Hb 150 grams/liter mmol/liter	Hb 150 grams/liter ml/dl	Hb 100 grams/liter mmol/liter	Hb 100 grams/liter ml/dl
13.3	100	97.7	8.88	19.9	5.98	13.4
12.0	90	96.9	8.84	19.8	5.94	13.3
10.6	80	95.7	8.71	19.5	5.85	13.1
9.3	70	93.8	8.53	19.1	5.71	12.8
8.7	65	92.4	8.39	18.8	5.63	12.6
8.0	60	90.6	8.21	18.4	5.49	12.3
7.3	55	88.2	7.99	17.9	5.36	12.0
6.7	50	85.0	7.68	17.2	5.13	11.5
6.0	45	80.7	7.32	16.4	4.91	11.0
5.3	40	74.9	6.79	15.2	4.55	10.2

Figure 2.—The normal hemoglobin (Hb)-oxygen dissociation curve is given at normal temperature and pH: note the 3 parts of the curve: the steep part where a small change in arterial oxygen tension (Pa_{O_2}) causes a large change in saturation (Sa_{O_2}) and oxygen content; the flat part where a large change in Pa_{O_2} causes a small change in saturation and content; and the intervening shoulder. The crosses at Pa_{O_2} 55 and 60 mm of mercury (7.3 and 8.0 kPa) identify the zone used by Medicare for supporting oxygen therapy in the home. In the columns to the right of the curve, note the deleterious effect of anemia on oxygen content.

criterion after experts argued that the old criterion (Sa_{O_2} of 85% or less) was too strict.[8] Clinical (pulse) oximeters measure the Sa_{O_2} noninvasively.[14] Some experts think, however, that oximeters are too inaccurate—the typical error range is 4%—to make decisions about long-term therapy.[15] For example, a Pa_{O_2} of 54 mm of mercury (7.2 kPa) (Sa_{O_2} 88%) meets the criterion, but a reading of 90%—within error—in the absence of a measured Pa_{O_2} does not. A susceptibility to erroneous readings, especially when carboxyhemoglobin is present, also limits the usefulness of oximetry.[14] A conservative approach is to use the Pa_{O_2} when deciding to start or stop oxygen therapy and to use pulse oximetry when monitoring Sa_{O_2} during sleep and when temporarily lowering or discontinuing oxygen until the Pa_{O_2} is tested.[7]

Substantial hypoxemia (Pa_{O_2} of 55 mm of mercury or less; Sa_{O_2} 88% or less) may develop only during sleep or exercise in some patients. Experts have recommended oxygen therapy during these activities with the hopes of preventing cor pulmonale,[11,16] but the evidence is limited. For example, the observation that patients with COPD and nocturnal oxyhemoglobin desaturation have greater hemodynamic abnormalities during rest and exercise than do patients without nocturnal desaturation supports the recommendation.[17] On the other hand, that the prognosis of patients with COPD was unaffected by not having nocturnal oxygen therapy is against the recommendation.[18] Controlled studies indicate that oxygen therapy increases exercise endurance and may relieve dyspnea in patients with COPD[19,20] and interstitial lung disease[21] who have exercise-related hypoxemia. Until there is more evidence to the contrary, HCFA supports the use of oxygen therapy only during the periods of hypoxemia.

Application

Enter the test date and results obtained with the patient breathing room air on the appropriate line depending on the test conditions as follows:

Line 1. If the Pa_{O_2} is 56 to 59 mm of mercury (7.4 to 7.8 kPa) or if the Sa_{O_2} is 89%, the findings of hypoxic organ dysfunction such as cor pulmonale, P pulmonale, and polycythemia should be checked in section 1. If the Pa_{O_2} is 60 mm of mercury (8.0 kPa) or greater or the Sa_{O_2} is 90% or more, the carrier must disallow the claim. See the discussion on "compelling medical evidence."

Lines 2 and 3. If hypoxemia occurs only during walking, sleeping, or exercising, Medicare supports therapy only during those "special conditions."

Line 4. Other conditions may include concomitant therapy with a mechanical ventilator or nasal continuous positive airway pressure generator.

Section 3B—Explanation if Tested Under Conditions Other Than Room Air

Background

Testing patients while they are breathing room air simplifies the task of the nonphysician reviewers. It may be inappropriate to permit a patient to undergo profound hypoxemia, for example, if the Pa_{O_2} is barely adequate with large flows of oxygen.

Application

Describe briefly the rationale for doing tests while the patient is receiving supplemental oxygen.

Section 3C—Name and Address of Test Provider

Background

The Health Care Financing Administration is concerned about possible conflict of interest. The persons testing the need for oxygen therapy must not be those providing that therapy—that is, the fox should not guard the hen house.

Application

The vendor or anyone associated with the vendor may not perform the arterial blood gas or oximetry tests.

Section NOTE—Compelling Medical Evidence

Background

Nonphysician reviewers will disallow claims when the usual criteria are not met. For example, the claims of the following three patients with a Pa_{O_2} of 61 mm of mercury (8.1 kPa), which is "too high," would be disallowed: Patient 1 lives 1,524 m (5,000 ft) higher than the blood gas laboratory; patient 2 has advanced interstitial lung disease and was receiving oxygen at 4 liters per minute when the Pa_{O_2} was measured; and patient 3, who receives maximal therapy for angina pectoris, showed improved exercise tolerance on supplemental oxygen. The reviewers may not understand that the Pa_{O_2} would fall into the qualifying range if patient 1 were tested at a higher altitude, that profound hypoxemia would certainly occur if patient 2 stopped supplemental oxygen, and that moderate hypoxemia may aggravate the angina afflicting patient 3. Patients and vendors usually urge the physician to submit a new Certificate of Medical Necessity, which often is disallowed again.

Application

Write a concise explanation on letterhead, provide supportive information, and request a review by the carrier's medical staff. It may help to inform the patient and vendor about this review.

Section 4—Oxygen Flow and Duration of Use

Background

The information on oxygen flow rate and duration is used to prorate reimbursement. Gross underestimates of flow and duration may severely limit reimbursement and lead to inadequate therapy. The hypoxemia of COPD usually responds well to low (less than 5 liters per minute) flows of oxygen. Most (93%) stable patients with COPD require 1 to 3 liters per minute at rest, and the most common flow is 2 liters per minute.[2,12,22] Low flows are tolerated well through a nasal cannula ("prongs"), aggravate alveolar hypoventilation infrequently, and are provided at home easily. The flow should raise the Pa_{O_2} into the ideal range of 61 to 70 mm of mercury (8.1 to 9.3 kPa) or the Sa_{O_2} to 91% to 94%.

Hypoxemia frequently worsens during sleep or exercise. Some patients who have normal oxygenation at rest require supplemental oxygen only during these activities. Experts advise patients who have hypoxemia at rest to raise the oxygen flow by an additional liter per minute during sleep or exercise.[1,22]

Application

Enter the liter-per-minute flow(s) and indicate the hours during which oxygen should be used—continuously (24

hours a day) or during specific activities. "Sleeping" should be for at least 12 hours because this duration of nocturnal oxygen therapy was shown to reduce mortality.[1] "Walking" implies ambulation outside the home, while "exercise program" implies the use of exercycles and calisthenics. The designation "prn" (for "as needed") is unacceptable.

Section 5A—Oxygen Equipment Prescribed: Supply System

Background

The new policy simplifies reimbursement, pays a flat rate for stationary equipment, and provides a small supplement (about $40 a month in Salt Lake City) for portable equipment. If equipment is not specified, the vendor may provide inconvenient (less expensive) equipment and not provide portable equipment. The consequences are using oxygen only part-time, which is less beneficial than continuous use,[1] worsening pulmonary hypertension when off oxygen therapy,[23] and becoming "shut in" and tethered to stationary equipment. Physicians should choose the equipment because it affects compliance with therapy, physical activity, and attempts at rehabilitation.[6-8,24-27]

Cylinders of compressed gaseous oxygen are ubiquitous. Most are made of heavy steel and hold small volumes of oxygen under high pressure—as much as 2,200 pounds per square inch (psi; 15,400 kPa). Typical stationary equipment used in the home includes a large (size H or K) cylinder, a flow regulator, and a dolly to support and move the cylinder safely. The H or K cylinder is about 1.5 m (5 ft) tall, weighs 68 kg (150 lb), holds 6,900 liters, and lasts less than 2.5 days at 2 liters per minute continuously. Portable equipment used outside the home during ambulation includes a small (size E) cylinder, regulator, and small dolly; this weighs about 9 kg (20 lb), contains 600 liters, and lasts about five hours at 2 liters per minute. When available, aluminum cylinders are lighter. Half-volume (D) cylinders weigh only about 4 kg (9 lb) and are convenient for patients who use low flows or conservers (see below). Patients usually do not fill cylinders because the high pressures are dangerous. Instead, empty cylinders are traded for full ones, causing problems with storage and delivery.

Liquid oxygen is compact—1 liter of liquid equals about 860 liters of gas—and the equipment is light. It is stored under low pressure (20 or 50 psi [140 or 350 kPa]) in special insulated reservoirs and boils slowly into gas. A typical stationary reservoir is about 1 m (3 ft) tall, weighs about 64 kg (140 lb), and contains enough oxygen to last a week at 2 liters per minute. Liquid oxygen is easily transfilled (transferred) to a miniature portable reservoir made by the same manufacturer (compatibility of connectors is a problem)[27] that weighs about 4.5 kg (10 lb) and lasts eight hours at 2 liters per minute. A compact version weighs about 3.2 kg (7 lb) and lasts half as long. Liquid oxygen may be available only in cities, becomes too expensive at flows over 3 liters per minute, and boils away even when the equipment is turned off.

A concentrator obtains oxygen from air with a zeolite molecular sieve. A typical concentrator looks (and sounds) like a small refrigerator, weighs 16 to 27 kg (35 to 60 lb), and has wheels for moving around the house. The more compact and quiet enricher uses a semipermeable membrane to provide 40% oxygen—the compensatory triple flow becomes disagreeable when oxygen requirements exceed 2 liters per minute. Concentrators and enrichers require electricity, operate under low pressure, cannot fill cylinders, and are usually not portable. Cylinders of oxygen are required for ambulation, power failure, and equipment malfunction. A small cylinder system is usually adequate, but an additional large cylinder emergency system is recommended where there are delays in restoring power or repairing equipment and for high flows that quickly deplete a small cylinder. Home oxygen delivery equipment has been described in detail elsewhere.[13,22,27]

Application

Choose equipment by need, availability, and cost.

Stationary source. Vendors and payers prefer concentrators because costs are low and the patient pays for the electricity (about $50 a month). Concentrators are best for nonambulatory patients who leave home infrequently. Patients may walk in confined areas with a 15-m (50-ft) oxygen extension hose or move the concentrator to a different room. Cylinders are best for nonambulatory patients who use low flows, such as 1 liter per minute, only during sleep or who live in areas with unreliable electrical power where concentrators are not feasible. Liquid oxygen is best for active patients who use oxygen continuously and leave home several times a week.[8] Some active patients who have exercise-related hypoxemia may also benefit from liquid oxygen.

Portable or ambulatory source. Prescribe portable equipment for patients who use oxygen continuously—that is, who have resting hypoxemia, or those who have exercise-related hypoxemia. Use small cylinders with a concentrator and a large-cylinder stationary system, or use a portable reservoir with a liquid oxygen stationary reservoir.

Section 5B—Oxygen Equipment Prescribed: Delivery System

Background

By convention, a nasal cannula is used with continuous flow therapy for comfort and convenience. Oxygen conservers are novel devices that extend oxygen supplies by about 50%, offer longer ambulatory times with portable equipment, and allow vendors to make fewer deliveries.[27,28] Pulse (demand valve) systems deliver oxygen only during inspiration and reduce waste during expiration. Reservoir systems save some of the oxygen delivered during expiration in a chamber adjacent to the nose (reservoir cannula) or on the chest (reservoir pendant), while a transtracheal catheter stores it in the trachea. Demand valves are set to the same conventional flow, while reservoirs and a transtracheal catheter use lower flows that are determined by monitoring the Pa_{O_2} or Sa_{O_2}.

Medicare has not developed a consistent policy for conserving devices. For example, our carrier supports the transtracheal catheter but does not support the reservoirs or demand valve. The new half-rate payment policy for flows less than 1 liter per minute discourages the use of reservoirs and transtracheal catheters that operate with lower flows. Medicare may modify its policy when it better understands the value of conserving devices.

Other ways to deliver oxygen include a tracheostomy adapter, tracheostomy mask, ventilator connector, and nasal continuous positive airway pressure adapter. A pulmonologist or respiratory therapist may offer valuable advice for working with this special equipment.

Application

Select the delivery system. Indicate the new lower flow for reservoir and transtracheal conserving systems.

Section 6—Description of Activities That Require a Portable System

Background

As noted earlier, portable oxygen equipment is needed to maintain therapeutic benefit in patients who are hypoxemic at rest or who have exercise-related hypoxemia. Mobility is important to maintain conditioning and social activities.[10,13,22,27] The failure to use oxygen when away from home reduces therapeutic benefit and increases the risk of morbidity and mortality. Medicare requires justification of the added expense.

Application

Indicate briefly that portable oxygen is required to maintain therapeutic benefit when away from home and specify the hours to be spent walking, exercising, or traveling.

Recertification and Retesting

The following guidelines became effective July 1, 1991. Physicians are required to submit a renewed Certificate of Medical Necessity based on the estimated duration of need that was indicated in Section 2. This must be done in the 3rd month, 9th month, and annually for the estimated durations of need of 1 to 3 months, 4 to 12 months, and lifetime, respectively. Retesting is required in the third month if the initial Pa_{O_2} is at or above 56 mm of mercury or the Sa_{O_2} is at or above 89%. Subsequent retesting is not mandatory but should be reported when performed.

Other Considerations

Always provide optimal medical therapy that includes the cessation of smoking, the appropriate use of bronchodilators, antimicrobials, and corticosteroids, and the treatment of problems known to aggravate hypoxemia, such as congestive heart failure.[11,13,16,22]

When home oxygen therapy is started in the hospital, the Certificate of Medical Necessity should be completed before discharge.[8] Physicians should use the technical expertise of respiratory therapists who have worked closely with their patients. Indeed, a respiratory therapist who works for the physician or medical center may now complete the form for later physician review and signature. The major advantage of careful discharge planning is that the vendor, often a respiratory therapist, will have enough time to train the patient and family in the proper use of equipment. Patients will also have a chance to learn the benefits of oxygen therapy: to prevent heart damage and other complications, improve mental and muscle function, and prolong life.[13,22] Finally, patients should be advised to use oxygen as prescribed to obtain full benefits of therapy and avoid misguided attempts to use less than prescribed flows or to use it only "as needed."

It is sad that the new Medicare policy and reporting form are a response to past abuses that had reached "scandalous" levels.[29] Physicians should send complaints and recommendations to HCFA if the oxygen policy continues to be burdensome.[8]

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Screening Persons Aged 65 and Older for Coronary Heart Disease Risk Factors

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Because of limited clinical investigations addressing the effectiveness of intervention to reduce known risk factors, it is difficult for primary care physicians to decide on which coronary heart disease risk factors to continue to screen for among older patients. The recently published report of the United States Preventive Services Task Force, using explicit screening criteria, has recommended that several risk factors be investigated for use among older adults. Recent longitudinal studies have found that a number of risk factors persist with advancing age—hypertension, left ventricular hypertrophy, impaired glucose metabolism, elevated cholesterol levels, obesity, smoking, physical inactivity, decline in vital capacity, and increased heart rate. Screening to identify many of these risks and treatment and counseling to modify them appear to improve survival. Evidence is less clear that diabetes mellitus and elevated cholesterol levels have the same significance for men and women as they age. Left ventricular hypertrophy and diabetes seem particularly important as risk factors for older women, whereas a high heart rate may be a greater risk for men.

(Kligman EW: Screening persons aged 65 and older for coronary heart disease risk factors. West J Med 1992 Jan; 156:45-49)

For those aged 65 years and older, coronary heart disease (CHD) remains the leading cause of death, accounting for almost 50% of all deaths in persons aged 85 and older.[1] As patients live longer, primary care physicians are faced with the difficult task of deciding which CHD risk factors to continue to screen for. A number of important questions remain unanswered: Are risk profiles different for the young compared with the old? Will the modification of risk factors in the elderly lead to improved survival? Are certain risk factors more significant for older women or older men? Because CHD is not an inevitable effect of the aging process,[2,3] it is important for physicians to take a comprehensive preventive approach through selected screening and counseling of geriatric patients to prevent its development or progression.

Even though chronologic age represents the most dominant determinant of risk as the incidence of CHD rises progressively with advanced age (especially among women),[2] recent research findings from longitudinal studies have helped to document the relative influence and strength of certain modifiable risk factors on CHD: hypertension, left ventricular hypertrophy, glucose metabolism, decline in vital capacity, obesity, elevated cholesterol levels, cigarette smoking, physical inactivity, and increased heart rate.

Further, the United States Preventive Services Task Force has recently published recommendations addressing the efficacy of screening tests and the effectiveness of early detection for most of these risk factors.[4] These recommendations were developed over four years by a panel of 20 experts from medicine and related fields, who reviewed evidence from 169 interventions to prevent 60 different illnesses and conditions in asymptomatic persons. Many of these interventions were screening tests for coronary heart disease. The efficacy of screening and the effectiveness of early detection in preventing or delaying the progression of disease were used as criteria to determine whether or not a particular risk factor should be screened for. "Efficacy" was defined as the test's accuracy (sensitivity, specificity, and predictive value) and reliability (reproducibility of test results). "Effectiveness" was defined as the test's value in detecting early a condition leading to an asymptomatic patient benefiting from treatment.

In this article I review those risk factors reviewed by the US Preventive Services Task Force (hypertension, type II diabetes mellitus, obesity, cholesterol, smoking, physical inactivity) in addition to others that have been identified through longitudinal studies (left ventricular hypertrophy, heart rate, and vital capacity) as predictors of coronary heart disease risk in adults aged 65 and older (Table 1).

TABLE 1.—*Screening for Coronary Heart Disease Risk Factors for Persons Aged 65**

Risk Factor	*Men*	*Women*	*US Preventive Services Task Force†*	*Intervention Efficacy*
Hypertension	++	++	Yes	++
Left ventricular hypertrophy	–	–	NA	–
Impaired glucose metabolism	+	++	Yes‡	–
Reduced forced vital capacity	–	–	NA	–
Obesity	++	++	Yes	–
Elevated cholesterol level	+	+	Yes	–
Lipid subfractions status	+	–	NA	–
Smoking	++	++	Yes	++
Physical inactivity	++	++	Yes	+
Increased heart rate	+	–	NA	–

*– = insufficient evidence exists, + = some evidence exists, ++ = strong evidence exists, NA = not addressed

†From US Preventive Services Task Force.[4]

‡High-risk group only.

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ABBREVIATIONS USED IN TEXT

CHD = coronary heart disease
ECG = electrocardiography
FVC = forced vital capacity
HDL = high-density lipoprotein
LDL = low-density lipoprotein

Hypertension

Screening Test: Annual Blood Pressure Measurement

The prevalence of hypertension (systolic blood pressure ≥ 160 mm of mercury or diastolic blood pressure ≥ 95 mm of mercury) among women aged 65 and older is about 50%, whereas the prevalence among men is 30%, increasing to 42% by age 75.[5] About a fifth of the population older than 65 has not had a blood pressure measurement within the past 12 months.[6] Yet, after age 65, systolic hypertension is the strongest reversible CHD risk factor and the only risk increasing in strength with advancing age. Results of the European Working Party on High Blood Pressure in the Elderly Trial showed that CHD mortality was strongly associated with increasing systolic hypertension (> 160 mm of mercury) for men and women.[7] The upper limits of blood pressure considered normal for the elderly without an increased CHD risk was found to be a systolic pressure of 160 mm of mercury and a diastolic pressure of 90 mm of mercury. Although there was a substantial decrease in cardiovascular morbidity and mortality with treatment, that benefit could not be shown for patients older than 80 years with diastolic hypertension (> 90 mm of mercury). A longitudinal study of 16,936 Harvard alumni aged 35 to 74 revealed that men with hypertension had more than twice the risk of CHD as normotensive men.[8] In the Framingham Heart Study, isolated systolic hypertension was found to predispose older men and women to cerebrovascular disease as well.[2] Recently published results from the Systolic Hypertension in the Elderly Program, a large, five-year, multicenter clinical trial, indicate that antihypertensive stepped-care drug treatment can reduce the incidence of major cardiovascular events and stroke by 36%.[9] There was no substantial reduction in cardiovascular mortality or the number of cardiac deaths, however.

Hypertension acts synergistically with other risk factors such as smoking and elevated cholesterol levels to greatly increase the CHD risk in older adults. Older patients with both diabetes and hypertension are also at a greater risk of renal disease, diabetic retinopathy, and cerebrovascular disease. Hypertension is twice as prevalent in obese persons.

The US Preventive Services Task Force recommends that all persons aged 65 and older have annual blood pressure screening.[4] Strong evidence exists that treating hypertension in men and women effectively improves survival and decreases morbidity from CHD.[7]

Left Ventricular Hypertrophy

Screening Tests: Electrocardiography and Echocardiography

Left ventricular hypertrophy is more prevalent among the elderly and is highly correlated with systolic hypertension.[10,11] It is also associated with increased CHD morbidity and mortality. Coexisting hypertension and left ventricular hypertrophy also place patients at increased risk of ventricular arrhythmias.[12] The prevalence of left ventricular hypertrophy among adults in the original Framingham Heart Study cohort aged 59 through 90 was 33% in women and 23.7% in men.[10] In that study, the presence of left ventricular hypertrophy was a better predictor of CHD than was high blood pressure. As determined by electrocardiography (ECG), definite left ventricular hypertrophy seems a stronger risk than that determined by voltage criteria, and the presence of nonspecific ST and T wave changes appears to add risk, especially in older women.[2] Electrocardiography, however, is not a sensitive tool for identifying anatomic hypertrophy and usually detects left ventricular hypertrophy only when the condition is severe. Although the echocardiogram is much more sensitive in detecting left ventricular hypertrophy at an earlier stage, it is considerably more costly,[11] and serial tests are not covered by Medicare and most third-party insurers.

The US Preventive Services Task Force does not recommend screening for this condition.[4] Further, there is insufficient evidence that modifying left ventricular hypertrophy will improve survival or provide any other benefit. Routine screening for this disorder by ECG or echocardiogram is not indicated at this time for asymptomatic older adults. The treatment of systolic hypertension (the most likely cause) to decrease cardiovascular morbidity and mortality is indicated.

Impaired Glucose Metabolism

Screening Tests: Fasting Glucose Measurement

As many as 30% of adults older than 65 may be glucose intolerant (fasting glucose level of 6.38 to 7.72 mmol per liter).[6] Macrovascular complications such as CHD and stroke are more likely to develop in these persons, but non-insulin-dependent diabetes mellitus is likely to develop in only 20%. The prevalence of diabetes mellitus (fasting glucose level > 7.77 mmol per liter) in adults aged 65 to 74 is 20%; this increases each decade of life[13] and reaches 40% by age 85.[14] Impairment of glucose metabolism does not progressively increase with age.[15] Nevertheless, there is a strong CHD risk association with glucose intolerance (for older women in particular).[2] Diabetes mellitus remains an extremely important CHD risk factor for both sexes. Hyperinsulinemia may have a more important role in atherogenesis than impaired glucose tolerance.[16] Two recent studies have shown that an "atherogenic" cardiovascular risk factor profile may precede the diagnosis of both non-insulin-dependent diabetes mellitus and impaired glucose tolerance.[16,17]

The US Preventive Services Task Force recommends screening only for those patients aged 65 or older with marked obesity, a family history of diabetes mellitus, or women with a history of gestational diabetes. Nevertheless, screening for impairment in glucose metabolism seems prudent for all older patients, especially those with other CHD risk factors. About 20% of older adults with diabetes may be asymptomatic. Early detection through screening may delay the progression of diabetes and the occurrence of complications. Among the elderly, the primary prevention of diabetes may be more important than screening. Weight loss and exercise have been shown to be effective in reducing two important risks for developing diabetes: obesity and glucose intolerance.[4] Even though physicians should initiate nutrition and exercise counseling for all patients aged 65 or older, those with impaired glucose metabolism as determined by a screening fasting glucose level should receive more substantive advice and monitoring. Such counseling may also lead to improvements in lipid profiles and insulin sensitivity, thus

reducing other risks for CHD.[18] Few trials have looked at the efficacy of nutritional counseling by physicians to reduce weight among older patients. In a recent six-month trial (Health Watch of Arizona Study), overweight older adults receiving counseling by their primary care physician decreased body fat on the average by 4.6% compared with a control group without counseling.[19]

Vital Capacity

Screening Test: Spirometry

Forced vital capacity (FVC) normally decreases with advancing age, but obesity and smoking exacerbate that progressive decline.[20,21] The decline in FVC among smokers appears dose-related. The loss of pulmonary function is slowed among smokers who quit, approaching the FVC values of nonsmokers.[20] In a longitudinal study of men younger than 74, body weight gains intensified the expected loss of FVC with age. With greater increases of body mass index—and, thus, adiposity—over time, the loss of FVC was greater. This effect may be accounted for by the role of adipose tissue in changing the position of the diaphragm and increasing chest wall resistance. No studies have looked at the effects of weight loss on slowing the rate of loss of FVC.

A low FVC was a strong predictor of cardiovascular mortality in the Framingham Heart Study and was correlated with a loss of muscle strength as assessed by hand grip. The association of FVC with CHD incidence was four times stronger among women than men after age 65.[2]

The US Preventive Services Task Force does not address the issue of screening for FVC. Screening for FVC is not indicated, with insufficient evidence currently available documenting the effectiveness of interventions. Ongoing clinical activity to encourage smoking cessation and weight loss for obese patients is indicated and may lead to improved FVC.

Obesity

Screening Test: Annual Body Weight

It is estimated that 24% of women and 14% of men younger than 75 are obese, or 20% above desirable weight.[22] Cumulative follow-up data from the Framingham Heart Study have identified body weight as a strong and independent risk factor for CHD.[2] Using the 1959 Metropolitan Life Insurance Company tables, any weight greater than 120% of ideal body weight was associated with increased coronary event rates. This risk association was present for both sexes, young and old, and rose in proportion to increases in weight. Obesity is strongly correlated with other CHD risk factors such as diabetes mellitus, hypertension, and elevated cholesterol levels.

The US Preventive Services Task Force recommends periodic measurement and evaluation of height and weight for all adults. Nutrition and exercise counseling is recommended for all patients 20% or more above ideal weight.

Elevated Cholesterol Levels

Screening Test: Lipid Profile

Because atherosclerosis develops by the third decade and progresses throughout life, whether to screen and subsequently intervene to decrease cholesterol levels in the elderly is a major question. Although the prevalence of hypercholesterolemia (6.21 mmol per liter and above) decreases with age, it is present in about a third of men aged 65 to 74 and half of women aged 65 to 74.[23] About 75% of adults older than 65 have had a cholesterol measurement within a five-year period.[6]

Total cholesterol level as a relative risk decreases in strength by 38% as a CHD risk predictor with age.[2] As an attributable risk, cholesterol levels remain a strong predictor.[24] Total cholesterol and lipid fractions progressively decline after age 50 in men but continue to rise in women until age 70 before declining. Mean high-density-lipoprotein (HDL)-cholesterol values remain stable for both sexes with advancing age. Numerous studies have identified HDL cholesterol as a more accurate predictor of CHD risk, especially among the elderly.[25-28(p5),29] Low-density-lipoprotein (LDL)-cholesterol and HDL-cholesterol measurements are of less predictive value for women, but these lipid fractions and the LDL:HDL ratio are significantly predictive of CHD in men when stratified by HDL-cholesterol levels.

The National Cholesterol Education Program recommends screening all patients without an age-based cutoff.[30] The US Preventive Services Task Force concluded that the periodic measurement of total serum cholesterol levels in the elderly was clinically prudent.[4] Insufficient data exist from clinical trials, however, to prove that the treatment of elevated cholesterol levels will lead to increased survival and a decreased prevalence of CHD in the elderly.

Baseline screening lipid fractions seem especially important for older men. In terms of counseling older patients with elevated cholesterol levels, the effects of dietary intervention, physical activity, and smoking cessation on lipid levels should always be discussed before considering control by medications. It is also useful to identify other medications patients may be taking that could cause cholesterol levels to rise such as β-blockers and diuretics.

Smoking

Screening Test: Patient History

The incidence of smoking among persons older than 65 is 19% for men and 13% for women.[31] Smoking remains a substantial risk factor for coronary death, but its predictive power decreases with advancing age.[2] Within the Framingham population, lifelong smokers who quit after age 65 did not have a decrease in coronary heart disease risk. The Chicago Stroke Study, however, a prospective longitudinal study of 2,674 people aged 65 to 74, found that CHD risk was lowered substantially for elderly ex-smokers quitting within the past five years.[32] Current cigarette smokers had a risk of death from heart disease 52% higher than nonsmokers. The excess risk of mortality declined within one to five years after smoking cessation. In another study of men and women older than 55 with angiographically documented coronary artery disease, the six-year mortality rate was almost two times greater for continuing smokers than for those who quit smoking before the study began. There was also a higher risk of myocardial infarction among those who continued to smoke.[33] Paffenbarger and co-workers found that smokers had an 84% increased risk of cardiovascular mortality over their lifetime.[8] In association with other CHD risk factors such as hypertension and elevated cholesterol levels, smoking also has a synergistic effect on the progression of atherosclerosis and CHD.

The US Preventive Services Task Force recommends screening all adults older than 65 for tobacco use and offering smoking cessation counseling to all patients using tobacco products.[34] The effectiveness of physician counseling in mo-

tivating patients to stop smoking depends on many factors. A meta-analysis of 39 clinical trials found the average rate of cessation to be 8% after six months and 6% after a year among unselected patients.[35]

Physical Inactivity

Screening Test: Patient History

The incidence of physical inactivity among persons older than 65 is 59% for men and 72% for women.[30] Only 8% of older adults participate in regular activities at least 20 minutes three or more times per week.[35] A 28% lower all-cause mortality rate was found among men younger than 74 who expended 2,000 or more kcals during exercise per week compared with less active men.[8] The strongest and most significant decline was in CHD mortality. By age 80, the amount of additional life attributable to adequate exercise begun at age 65 compared with persistent sedentariness was two years. In an Adventist Mortality Study that observed more than 9,000 men for 30 years, moderate physical activity was shown to be protective to age 95.6 for all-cause mortality and to age 83.9 for CHD.[36] Exercise also has an important protective role in reducing other CHD risk factors such as hypertension, diabetes, glucose intolerance, obesity, and smoking.[37,38] High-density-lipoprotein–cholesterol levels appear to increase favorably in the elderly undergoing regular exercise training.[39] The effect of exercise on lowering LDL-cholesterol levels is less clear but may occur among older master athletes compared with a sedentary control group.[40] Physical inactivity may also be a marker for other medical problems such as congestive heart failure, chronic obstructive lung disease, or depression.

Evidence exists that exercise and physical fitness after age 65 are cardioprotective. Data from clinical intervention trials suggest that modifying a sedentary life-style will decrease CHD progression.[41] The US Preventive Services Task Force recommends that all adults aged 65 and older be screened regarding their physical activity and that appropriate counseling be provided on how to perform exercise safely.[4,34]

Heart Rate

Screening Test: Resting Heart Rate

A high resting heart rate has been shown to be an important risk variable for men, old and young, but not for women.[2] An increased heart rate may identify those at risk because of cardiac dysfunction, increased sympathetic activity that may exacerbate CHD, or physical inactivity.

The US Preventive Services Task Force does not address whether the heart rate should be periodically assessed. Nevertheless, identifying high resting heart rates (>90 beats per minute) among men aged 65 and older is an integral component of the cardiovascular examination.

Concluding Comments

Limited evidence from epidemiologic studies and controlled clinical trials suggests that modifying certain CHD risk factors in the elderly will improve overall survival and decrease the prevalence of CHD. Most screening and intervention activities are not costly and should be an integral part of health care maintenance and physician-initiated preventive medicine recommendations. The decline in mortality from cardiovascular diseases over the past 30 years among all age groups appears most highly correlated with the lowering of serum cholesterol levels and systolic blood pressures and reduced cigarette smoking.[42] Screening older adults for traditional risk factors (hypertension, smoking, hyperlipidemia, and diabetes mellitus) identifies a tenth of the elderly population from which 21% of CHD cases arise.[5] Based on existing data, routine screening for systolic hypertension, impaired glucose metabolism (abnormal fasting glucose levels), hypercholesterolemia, physical inactivity, smoking, obesity, and high resting heart rate will increase the efficacy of CHD risk prediction. Current evidence, however, is insufficient to recommend routinely testing older adults for abnormal forced vital capacities or left ventricular hypertrophy.

Because the CHD incidence increases in the elderly, the short-term absolute effects of preventive measures may actually be greater in older than in younger people. Risk profiles are somewhat different for the young than for the old. Although the importance of hypertension, obesity, smoking, exercise, and heart rate persists with advancing age, evidence is less clear that diabetes and elevated cholesterol levels have the same significance for men and women as they age. Left ventricular hypertrophy and diabetes seem particularly important as risk factors for older women whereas an increased resting heart rate may be a greater risk for men. If all cardiovascular disease and cerebrovascular disease could be eliminated in persons older than 65, a 16-year gain in life expectancy could be anticipated.[5] This compares with an increased life expectancy of only 1.2 years if all cancers could be eliminated.[43] Improved quality of life through the reduction of CHD morbidity is of even greater importance.

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Articles

Health Behavior and Experiences of Physicians
Results of a Survey of Palo Alto Medical Clinic Physicians

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The results of a health practice questionnaire submitted to the 152 physician members of the Palo Alto Medical Clinic, 126 of whom responded, indicate a generally favorable profile of preventive medicine strategies. Physicians generally smoke less, drink about the same, exercise more, and use their seat belts more than the population at large. They also can expect to live longer. These results are compared with those of other physician surveys and surveys of the general public.

(Bortz WM II: Health behavior and experiences of physicians—Results of a survey of Palo Alto Medical Clinic physicians. West J Med 1992 Jan; 156:50-51)

Health is an inside job. The bulk of human illness is due less to extrinsic factors such as infections, toxins, and trauma than to health decisions. The Surgeon General of the United States estimates that 60% of physician visits, admissions to hospital, and deaths are due to preventable causes. The advice physicians give to patients often reflects their own health beliefs and status. Unfortunately, few studies report the health behaviors of physicians and other health professionals. To this end, a 30-item questionnaire was prepared in general conformance with the health prevention features in *Healthy People 2000.*[1] This was submitted to the 152 physician members of the Palo Alto Medical Clinic (PAMC), a large multispecialty group practice of 122 men (average age 49) and 30 women (average age 41).

Results

Some general health habits of the 126 respondents (83%) are presented in Table 1. In 1987, 29.1% of the American population smoked. In contrast, only 1.6% of the PAMC physicians do; 22% of the present sample had stopped compared with 33% nationally.[1] Most of the PAMC physicians (90%) consumed alcohol, 35% nightly. Wine and beer were the preferred beverages. Almost all wore seat belts regularly and had yearly physical examinations.

In all, 56 (44%) of the PAMC physicians reported being overweight; only 1 (0.8%) considered himself underweight (Table 2). Only five, however, reported themselves to be 15 lb or more overweight, and one was 75 lb too heavy. More than half (54%) were on a low-fat diet, while 39% said they restricted calories. One physician was on a low-gluten diet. Thirteen took supplementary vitamins, and 49 reported that they consciously tried to maintain an adequate calcium intake, either through dairy products or calcium supplementation.

Most of the physicians (93%) exercise regularly. In contrast, 60% of middle-aged Americans surveyed nationally reported a sedentary life-style, and less than 10% exercised aerobically.[2] Jogging, hiking, biking, and swimming were the most common forms of exercise in the PAMC sample. Six had run a marathon in the previous year. A total of 27% (34) reported being in better physical condition than a year before, and 13% considered themselves to be the same.

The average serum cholesterol level of the PAMC physicians was 198 mg per dl (512 mmol per liter) for the men and 160 mg per dl (4.14 mmol per liter) for the women. In 1978 the figure for the clinic physicians was 215 mg per dl (5.56 mmol per liter). In 1980, the general US population had a mean cholesterol level of 213 mg per dl (5.51 mmol per

TABLE 1.—*Basic Health Habits of 126 Physicians at Palo Alto (California) Medical Clinic*

			Indices of Health					
Physicians	*No. (%)*	*Average Age, yr*	*Smoker, No. (%)*	*Ex-smoker, No. (%)*	*Uses Alcohol No. (%)*	*Average Sleep, h/night*	*Wears Seat Belts, No. (%)*	*Yearly Physical Examination, No. (%)*
Men	98 (78)	49.6	2 (2)	25 (26)	89 (91)	7.1	95 (97)	84 (86)
Women	28 (22)	40.6	0 (0)	3 (11)	25 (89)	7.4	28 (100)	19 (68)

TABLE 2.—*Self-reported Nutritional and Exercise Data of 126 Physicians at Palo Alto (California) Medical Clinic*

	Nutrition Status					Exercise Status	
Physicians	*Overweight, No. (%)*	*Underweight, No. (%)*	*Dieting, No. (%)*	*Takes Vitamin Supplement, No. (%)*	*Extra Dietary or Calcium Supplement, No. (%)*	*Exercises Regularly, No. (%)*	*Some or Better Fitness Than Year Before, No. (%)*
Men, n=98	47 (48)	1 (1)	79 (81)	9 (9)	33 (34)	94 (96)	39 (40)
Women, n=28	9 (32)	0 (0)	14 (50)	4 (14)	16 (57)	23 (82)	11 (39)

From the Palo Alto Medical Foundation, Palo Alto, California.
Reprint requests to Walter M. Bortz II, MD, Palo Alto Medical Foundation, 300 Homer Ave, Palo Alto, CA 94301.

TABLE 3.—*Health Habits of Physicians*

Physician Group	Source	Smokes (Ex), %	Alcohol Use (daily), %	Average Sleep, h/night (%)	Exercises Regularly, %	Wears Seat Belts, %	Yearly Physical Exam, %	Overweight, %
PAMC	This study	1.6 (22)	90 (35)	7.3	93	98	81	43
PAMC	1978*	5	95	7.5	95	..	..	..
Harvard	Glanz et al, 1982[8]	<10 (33)	93	..	49	73	54	29
UCLA	Linn et al, 1986[4]	9	89 (9)	..	90	..	..	..
Temple	Glanz et al, 1982[8]	19 (19)	(13)	7-9 (75)	63	..	<25	..
Fresno	Wells et al, 1984[9]	15	(24)	..	73	..	..	59
Harvard	1982[10]†	14	90	..	75	..	..	..
United States	CDC, 1987[2]	29 (32)	..	..	40	24†	..	26

CDC = Centers for Disease Control

*Unpublished data.
†From Harvard Medical School Health Letter, 1982.[10]

liter).[1] The high-density-lipoprotein values of our group were 59 mg per dl (1.52 mmol per liter) for the men and 65 mg per dl (1.68 mmol per liter) for the women.

None of those reporting were currently hypertensive, but eight were under treatment for this condition. Nationally, 30% of the population has hypertension.[1] Of the PAMC physicians, 22 (13 men, 9 women) had been admitted to hospital in the preceding year, 5 for a surgical procedure. Of the 13 men admitted, 5 had orthopedic and 2 had urologic conditions. Of the 9 women admitted, 6 were for obstetric care. The average age of those admitted to hospital was 53 for men and 40 for women. Thus, of the 126 physicians, 13% had a nonobstetric admission during the preceding year. This is slightly higher than the national average.[3]

In all, 36% of the group took some medication in the preceding year: aspirin (14), hypolipidemic agents (10), nonsteroidal anti-inflammatory drugs (6), insulin (3), and β-blockers (4). A number of those taking aspirin were on a drug protocol, so the real incidence is lower.

The PAMC physicians rated their behavior A type on a scale of 0 to 10 as 6.7 for the men and 7.1 for the women as contrasted with our group value of 6.6 twelve years earlier (unpublished data, 1978). The PAMC physicians rated their personal happiness as 7.8 for the men and 8.0 for the women on a scale of 0 to 10. A survey of physicians at the University of California, Los Angeles, reported that their life satisfaction was slightly higher than a national average,[4] whereas 63% of a group of Massachusetts physicians said they were "happy" with their lives.[5]

The male members of the PAMC physician staff estimated that they would live to an average age of 86, the women estimated an average age of 82. All said that they would like to live two years longer than they expected to. In 1978, the group, with an average age of 49.9, expected to live another 31.7 years to 81.6 years. This is 7.7 years more than the national projection.[6(p71)] In 1940 physician mortality was the same as that of white men in the general population,[7] but by 1971, physicians were clearly surviving longer than men in general. The mortality rate of PAMC physicians is too small to be compared with any national average. Clearly this cohort of physicians expects to live longer than would normally be expected. The health behavior characteristics reported in this survey may actually allow that to occur.

Discussion

Table 3 gives a composite summary of seven reports on physician health habits, placed in context with the available national figures. The data are not all comparable and certainly are not simultaneous. The more recent figures from the PAMC with regard to smoking, for example, show a decreased prevalence from just 12 years ago. The other figures cited in Table 3 might reflect similar declines if retested now. By and large, however, it appears that physicians smoke less, drink about the same, exercise more, and use their seat belts more than the population at large. Hospital admission rates for the one-year period assessed were not different for the PAMC physicians from those for the national average.

Physicians' success in altering the health behavior of patients is highly related to their own health behavior.[9-12] Physicians should therefore always seek to serve as exemplars of the health practices that they would like to inculcate in patients, to promote their long-term mental and physical well-being.

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Conferences and Reviews

Current Issues Concerning the Epidemiology of Acquired Immunodeficiency Syndrome and Human Immunodeficiency Virus

Discussant
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This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

HOMER A. BOUSHEY, MD*: *Speculations about the spread of the acquired immunodeficiency syndrome (AIDS) into the general population cause widespread anxiety. Correcting these speculations and focusing concern on the appropriate settings require careful study of the epidemiology of human immunodeficiency virus (HIV) infection. Alan Lifson, MD, MPH, herein reviews what is known about the risks of HIV transmission and the development of AIDS. Dr Lifson's own work has been an important source of information, for his study of serum obtained from homosexual men participating in a trial of hepatitis B vaccine provided early important data on the cumulative risk of AIDS after HIV seroconversion. Dr Lifson has continued to work actively in studying HIV transmission and progression and will summarize some of his observations.*

National and International Epidemiology of AIDS and HIV Infection

ALAN R. LIFSON, MD, MPH†: Ten years ago, reports were published of homosexual men with two then uncommon illnesses: Kaposi's sarcoma and *Pneumocystis carinii* pneumonia.[1] As of August 1, 1991, a total of 186,895 cases of AIDS have been reported to the Centers for Disease Control, including 3,199 cases in children.[2] According to one estimate, by the end of 1993, a cumulative total of 390,000 to 480,000 cases of AIDS will occur, with 285,000 to 340,000 deaths.[3] In 1993 alone, between 61,000 and 98,000 cases of AIDS are expected to occur.

In addition to those men, women, and children with AIDS, many more persons are infected with HIV. The United States Public Health Service has estimated that in mid-1989, about 1 million people in this country were infected with HIV, with at least 40,000 new infections occurring each year among adults and adolescents.[3]

Cases of AIDS have been reported from every state in the country, with the greatest number from California, Texas, Florida, New York and New Jersey.[2] In San Francisco alone, as of August 1, 1991, a total of 10,837 cases of AIDS were reported, with 7,599 deaths; 163 cases and 165 deaths were reported during the month of July alone, representing more than 5 new cases and 5 deaths per day.[4] According to one projection, between 12,349 and 17,022 cumulative cases of AIDS will be diagnosed in San Francisco through June 1993.[5]

National surveillance data reinforce the fact that AIDS is a disease with a significant effect on young people; for example, 68% of all patients with AIDS are younger than 40 years.[2] In 1987, 11% of all deaths among men aged 25 to 44 were due to HIV-related causes, compared with less than 1% in 1980; data concerning other causes of mortality suggest that the proportion of HIV-related deaths for 1987 may have been even higher.[6]

Two populations in which AIDS and HIV infection are becoming increasingly evident are women and racial and ethnic minorities. Nationally, 11% of all cases occur in females; this proportion has been increasing over time. For example, from 1989 to 1990, reported cases of AIDS increased by 33% in women, compared with 22% in men.[7] According to one estimate, if current mortality trends continue, HIV infection or AIDS can be expected to become one of the five leading causes of death in women of reproductive age.[8]

The acquired immunodeficiency syndrome has also had a heavy effect on racial and ethnic minorities. For example, of adults with AIDS, approximately 28% are African American and 16% are Hispanic.[2] According to 1980 census data, however, about 12% of the population is African American and 6% is Hispanic; therefore, racial and ethnic minorities make up a disproportionately large share of the AIDS cases.[9] In children, the effect on minorities is even greater; of the children with AIDS, 78% are African American or Hispanic.[2] From 1989 to 1990, reported cases of AIDS increased by 28% in African Americans and 26% in Hispanics, compared with 20% in whites.[7]

It is also important to emphasize that AIDS is a worldwide epidemic of increasing proportions. Because of underreporting and underdiagnosis, many more cases of AIDS

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
IV = intravenous
WHO = World Health Organization

have occurred than are reported. According to an estimate from the World Health Organization (WHO), as of December 1990 the actual cumulative global total number of AIDS cases was more than 1.3 million, with about 400,000 cases in children; the greatest number of cases in both adults and children were from sub-Saharan Africa.[10] It is also estimated that between 8 and 10 million persons worldwide may be infected with HIV, with the highest rates of HIV infection again being in sub-Saharan Africa.[10]

Although in this review I will primarily focus on AIDS and HIV type 1, it should be noted that HIV-2 has also been reported from a number of areas, particularly in West Africa, and that this virus may also be associated with immunodeficiency and associated diseases.

Patterns of Transmission for HIV

Of adults with AIDS in the US, 59% are homosexual or bisexual men; 7% are homosexual or bisexual men who also report the intravenous (IV) use of drugs; 22% are women or heterosexual men who report the IV use of drugs; 1% are persons with hemophilia or other coagulation disorders; 2% are recipients of blood, blood components, or tissue; 6% are thought to have acquired infection through heterosexual intercourse; and for 4% the risk history is undetermined.[2] Among those persons thought to have been infected through heterosexual intercourse, 22% are from countries termed pattern II countries by the World Health Organization—including some countries in sub-Saharan Africa or the Caribbean—where most cases of AIDS are presumed due to heterosexual transmission.[2] The remaining cases are in persons who report heterosexual contact with a partner who is known to be HIV infected or a partner who is a member of a high-risk group.

Although homosexual and bisexual men still account for most AIDS cases, in recent years there has been an increase in the proportion of cases attributed to either heterosexual IV drug use or heterosexual contact. For example, between 1989 and 1990, reported cases of AIDS increased by 19% in homosexual or bisexual men, 24% in female or heterosexual male drug injectors, and (excluding those persons from pattern II countries) 40% in heterosexual contact cases.[7]

The distribution of risk factors can vary greatly in different areas. For example, in San Francisco, 95% of adults with AIDS are homosexual or bisexual men; this includes 9% of adults with AIDS who are homosexual or bisexual men who also report a history of injecting drugs.[4] In northeastern cities such as New York, the proportion of cases among heterosexual IV drug users is much higher.

Studies of AIDS patients whose risk history is undetermined suggest several major reasons for having "no identified risk."[11] Many of these are persons on whom no risk information is available; for example, they may have died or been lost to follow-up before a detailed risk evaluation could be done. Others may have refused to discuss their risk history or denied a history of high-risk sexual or drug use habits to the interviewer for personal, social, or other reasons. Finally, a person may have been infected through heterosexual contact, but if it was not known for certain that their sexual partner was HIV infected or a member of a high-risk group, they would be classified in the "risk history undetermined" category.

In this country, as well as for much of North America and Europe, most cases of AIDS occur in homosexual or bisexual men or drug injectors. In other countries—including many countries in sub-Saharan Africa—most AIDS cases are thought to have occurred as a result of heterosexual transmission. Patterns of transmission may be changing in many parts of the world. For example, in Central and South America, heterosexual transmission as a risk factor is becoming increasingly apparent.[12] In parts of Asia, where HIV was generally introduced later in the epidemic and fewer cases of AIDS have been reported to date, HIV infection has emerged in a number of populations, such as IV drug users and female prostitutes in Thailand[13,14] and prostitutes in certain cities in India.[15]

This brief review does not cover in detail the important subjects of HIV transmission in the health care setting and guidelines to prevent such transmission. I do note that health care workers have been reported to seroconvert after exposure to blood from HIV-infected patients. The great majority of such reports are in persons who received parenteral exposures, although the risk after such exposures is low.[16-18] There have also been a few reports of health care workers infected after contact of blood with open wounds, skin with breaks in it (for example, due to dermatitis or chapping), or mucous membranes.[19] A recent report described HIV infection in five patients without established risk factors who had procedures performed by an HIV-infected dentist who did not always follow recognized infection control guidelines.[20,21] DNA sequence analysis showed that the HIV strains from these patients were similar (although not identical) to each other and those of the dentist. The exposure that may have resulted in viral transmission to these patients could not be conclusively identified, and the precise mode of HIV transmission is uncertain. Other investigations of HIV-infected health care workers (such as surgeons) who performed invasive procedures have not found evidence of HIV transmission to their patients[22]; these and other data support the assertion that there is an extremely low risk of a patient acquiring HIV infection during an invasive procedure.[23]

In addition to an awareness of how HIV is transmitted, it is equally important to know how HIV is not transmitted. National surveys conducted in 1987 and 1988 showed an increasing proportion of persons saying that it was "very unlikely" or "definitely not possible" to acquire HIV through exposures such as eating in a restaurant where the cook had the AIDS virus, using public toilets, or working near someone with the AIDS virus.[24] At least a dozen studies have evaluated over 800 household or boarding school contacts of persons with AIDS or HIV infection and have not found evidence of transmission through such exposures.[25,26] For example, one study evaluated 206 household contacts of 90 persons with AIDS.[27] These contacts did not have additional risk factors for HIV infection; for example, they were not sexual partners of the HIV-infected persons or infants born to HIV-infected women. Personal contacts with the AIDS patients in some cases included sharing a bath or toilet, sharing household items such as towels and eating utensils, shaking hands, kissing on the cheek, and helping the person

to bathe, dress, or eat. None of the contacts were found to be seropositive for HIV antibody.

Of those children with AIDS, 84% have a mother who is either known to be HIV-positive or to belong to a high-risk group, 5% have hemophilia or other coagulation disorders, 9% have received blood or blood components, and for 2% the risk history is undetermined. An analysis of data for children whose risk history is undetermined also suggests that risk information (particularly concerning the mother) is often incomplete.[28] With respect to transmission from a woman to her newborn, infection is generally thought to occur in utero and possibly at the time of delivery; a few reports have also suggested the possibility of transmission through breastfeeding,[29,30] although the importance of this route of transmission remains to be determined.

Factors Facilitating Sexual Transmission

As previously mentioned, most adults with AIDS are thought to have acquired HIV infection through sexual transmission. Factors possibly facilitating such transmission include specific sexual practices, the clinical and immunologic status of the HIV-infected sexual partner, and the presence of other sexually transmitted diseases.

Among gay and bisexual men, the sexual practice most highly associated with HIV infection is receptive anal intercourse.[31] Although anal intercourse may also be associated with an increased risk of HIV infection among heterosexual couples, most HIV infection resulting from heterosexual contact has occurred among those who reported only vaginal intercourse.[32] Several case reports have also described HIV infection in association with receptive oral intercourse.[33,34] For example, a recent report described the cases of two men who seroconverted for HIV antibody and who reported no anal intercourse for at least five years preceding the estimated date of seroconversion.[33] Both men reported multiple episodes of receptive oral intercourse with ejaculation. Although other practices (such as unprotected anal intercourse) may be associated with a higher risk of HIV infection, receptive oral intercourse is therefore associated with a potential risk of HIV infection.

Studies have also suggested that sexual transmission is more likely to occur when the HIV-infected partner has clinical or laboratory evidence of immunodeficiency, such as AIDS or a low $CD4^+$ lymphocyte count.[35,36] This may be due to a greater viral burden and a greater number of virus-infected cells in the seropositive partner, increasing the likelihood of HIV transmission to a seronegative partner.

A number of studies have suggested that HIV transmission may be facilitated by the presence of other sexually transmitted diseases associated with genital ulcers, such as herpes, syphilis, or chancroid.[37] A possible reason is that genital ulcers may disrupt the skin or mucosal lining, thereby facilitating HIV transmission. Recent studies from Africa have also described nonulcerative sexually transmitted diseases as possibly promoting heterosexual transmission. For example, gonorrhea and chlamydial infection were identified as risk factors for HIV infection among female prostitutes in Zaire.[38] Possibly these findings are due to cervicitis, either because of an increased number of target cells or because of cervical changes that increase the likelihood of HIV infection. It is clear that for many reasons, the control of sexually transmitted disease is integrally related to preventing the spread of HIV.

'Natural' History of HIV Infection

Many prospective studies have evaluated the prognosis of HIV infection, including the development of AIDS and other manifestations of HIV disease.[39] In one prospective cohort study of homosexual and bisexual men, the San Francisco City Clinic Cohort Study, the date of HIV seroconversion could be reliably determined for a subset of all seropositive men.[40] Among these men, the likelihood of AIDS developing was low for the first few years after HIV infection, with only 1% of infected men having progression to AIDS within two years of seroconversion.[41] The cumulative risk of AIDS then increased over time, with an estimated 12% of HIV-infected men having AIDS within 5 years, 53% within 10 years, and 61% within 11.8 years after HIV seroconversion (95% confidence interval, 56% to 66%).

Whether other factors besides the duration of HIV infection affect the likelihood of AIDS is an area of active investigation. In the laboratory, several infectious agents, such as certain herpesviruses, have been shown to affect the replication of HIV[42]; however, the existence of an infectious cofactor increasing the likelihood of progression to AIDS based on in vivo data remains uncertain. Other factors possibly affecting the progression of HIV infection to AIDS include genetic background (such as HLA type),[43] age,[44] characteristics of the viral strain or strains infecting a person (including cellular host range and pathogenicity), immunologic response to HIV infection (including $CD8^+$ suppressor cell activity),[45] and other infectious agents theoretically serving as cofactors. Possibly multiple factors, acting in a complex interrelationship, modulate the likelihood of specific manifestations of HIV disease developing.

A major factor affecting HIV disease progression may be the use of antiviral therapies such as zidovudine (AZT). Placebo-controlled studies have indicated that the use of zidovudine in either asymptomatic[46] or mildly symptomatic[47] HIV-infected persons with a $CD4^+$ count of less than 500 cells per μl decreases the rate of progression to AIDS or severe AIDS-related conditions. Based on these data, zidovudine is currently licensed to be given to HIV-infected people with a $CD4^+$ count of less than 500 cells per μl. Given the many who are estimated to be infected with HIV,[3] meeting the needs for antiviral and other prophylactic therapies is an important issue for those involved in planning health services and health care delivery.

Predictors of Outcome

One of the most important questions concerning the outcome of HIV infection is identifying those cases that are most likely to progress to AIDS. Studies have identified various signs and symptoms associated with an increased likelihood of progression. These include certain oral manifestations of HIV (such as oral candidiasis), the presence of certain signs and symptoms (such as fever or weight loss), and severe herpes zoster.[48-50] Although generalized lymphadenopathy may be associated with HIV infection, among those who are HIV infected, a number of studies have indicated that people with lymphadenopathy are not significantly more likely to have progression to AIDS.[48,49]

Certain laboratory tests may also help predict in whom AIDS is most likely to develop. One of the most important predictors is the $CD4^+$, or T-helper, count. Both the absolute $CD4^+$ count and the percentage of $CD4^+$ cells have been shown to have prognostic significance.[44,48,49,51] For example,

in the San Francisco General Hospital Study, of HIV-infected homosexual and bisexual men whose baseline $CD4^+$ count was 200 cells per μl or less, 87% progressed to have AIDS within three years; of those men with a baseline value of over 400 cells per μl, only 16% had progression to AIDS.[48] Other studies that looked at specific disease outcomes have shown that persons in whom *P carinii* pneumonia developed were likely to have low $CD4^+$ counts preceding their diagnosis.[52,53] Based on such data, the Public Health Service currently recommends prophylaxis against *P carinii* pneumonia for HIV-infected persons with a $CD4^+$ count of less than 200 cells per μl or less than 20% of the total lymphocytes.[54]

Other laboratory measurements besides the $CD4^+$ count have been shown to have prognostic importance for HIV disease progression. Two of the most powerful predictors have been p24 antigen and β_2-microglobulin; for example, studies have shown increased progression for persons with an assay positive for p24 antigen[44,48] or an elevated β_2-microglobulin level.[48,55] Various combinations of the $CD4^+$ count, p24 antigen, and β_2-microglobulin may have even greater predictive value. Studies have also suggested that the serum neopterin level may have prognostic value[51]; however, neopterin and β_2-microglobulin appear to be highly correlated, and the prognostic information from one assay may not be substantially improved by information from the second.

Survival

Of those adults diagnosed with AIDS, 64% are known to have died. Of those diagnosed in 1984 or earlier, however, more than 90% are known to have died[1]; additional persons may have died and not been reported to the AIDS surveillance system. Of those children diagnosed with AIDS, 52% are known to have died. For those persons in San Francisco whose AIDS was diagnosed from 1981 through 1989, the estimated median survival was 15.0 months.[56] The median survival rose, however, from 11.2 months for those diagnosed between 1981 and 1985 to 18.4 months for those diagnosed between 1987 and 1989. Studies in other areas (for example, in Washington State) have also identified increases in median survival.[57] There are a number of possible reasons for these changes, including an earlier diagnosis of AIDS, the use of antiviral therapies such as zidovudine, and other improvements in medical care.

Kaposi's Sarcoma

Surveillance data suggest that the distribution of AIDS-defining diseases may be different in different risk groups and that patterns of disease may be changing over time. A disease of particular interest is Kaposi's sarcoma. Among adults with AIDS, the proportion of homosexual or bisexual men with Kaposi's sarcoma is much greater than for other persons. In an analysis of US surveillance data for persons with AIDS, the percentage reported to have Kaposi's sarcoma ranged from 21% for homosexual and bisexual men to only 1% for persons with hemophilia; homosexual and bisexual men had a substantially higher risk of Kaposi's sarcoma than did any other transmission group.[58] In addition, national and San Francisco surveillance data[59,60] and data from well-characterized cohorts of homosexual and bisexual men[61] indicate a significant decline over time in the proportion of persons with AIDS who present with Kaposi's sarcoma.

Kaposi's sarcoma may differ from other AIDS-related illnesses in several ways. Analysis of data from the San Francisco City Clinic Cohort Study suggests that Kaposi's sarcoma may have a shorter incubation time (from HIV infection to diagnosis) and longer survival time (from diagnosis to death) than other AIDS-defining diseases.[61,62] This is consistent with other data indicating that AIDS patients with opportunistic infections tend to have lower $CD4^+$ counts than persons with Kaposi's sarcoma alone[63] and suggests that this disorder develops at an earlier stage of immune suppression than certain other AIDS-defining diseases.

Several studies have suggested that Kaposi's sarcoma may be associated with a cofactor that increases the likelihood of its development. An analysis of national surveillance data suggested that such a cofactor may be sexually transmitted.[58] If so, identifying such an agent will be important for helping to understand more about the pathogenesis of Kaposi's sarcoma and may have implications for both the prevention and treatment of this AIDS-related illness.

Conclusion

In this brief review I have addressed only some of the many important issues and unresolved questions concerning the epidemiology of AIDS and HIV infection. The acquired immunodeficiency syndrome continues to provide challenges to health care professionals in many areas. One such challenge is for health care professionals to serve as educators concerning the epidemiology of AIDS, including the ways HIV is and is not transmitted. By doing so, they assist not only patients and their families but members of the community who look to them for guidance.

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Pulse Oximetry and Capnography in Intensive and Transitional Care Units

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This is an edited summary from a combined Medical-Surgical Critical Care Conference at Harbor-UCLA Medical Center, December 19, 1990, and January 14, 1991.

Increasing concerns about the benefits and costs of intensive care units (ICUs) have prompted examination of the types of patients who are admitted and the patient care services provided.[1-3] Because a substantial proportion of ICU patients are admitted for monitoring only, there has been interest in identifying which patients can be safely and effectively admitted to intermediate care or "step-down" units, in which monitoring is performed noninvasively. This concept has become especially popular for patients with respiratory abnormalities, including respiratory failure, largely because of the development and introduction of noninvasive monitoring technology.[4,5]

Intermediate care units usually lack the personnel and equipment capabilities for invasive monitoring, substituting noninvasive methods to retain effective care. Some of these new monitoring techniques may be applicable to the "usual" ICU environment as well. It is our objective in this conference to describe the basic theory of operation, performance, and limitations of pulse oximetry and capnography. Although other instruments—such as transcutaneous oxygen and carbon dioxide probes, as well as tissue oxygen monitors—are available, they have not yet found wide acceptance and will not be discussed here.

Pulse Oximetry

Noninvasive monitoring of arterial blood oxygen saturation in the ICU is done almost exclusively with pulse oximetry. The evolution of this relatively new device has been outlined recently.[6] The pulse oximetry method allows the application of spectrophotometric techniques to useful clinical situations, overcoming such obstacles as the need to arterialize the vascular bed being measured and account for differences in skin pigmentation and tissue thickness. Technologic advances accelerating the development of these devices include the availability of small, high-intensity, nearly monochromatic light-emitting diodes (LEDs) that produce light at appropriate wavelengths and fast microprocessors that are needed to transform collected light absorbance data into estimates of relative oxyhemoglobin concentrations.

Principles of Pulse Oximetry

The principles of pulse oximetry are important to understand when considering the application of these devices to critical care. Most authors have described the pulse oximeter as using the Beer-Lambert law of light absorption. Some of the limitations of pulse oximetry can be appreciated by examining the assumptions implicit in this formula and the empiric adjustments made to it during pulse oximetry. According to the Beer-Lambert law, the absorption of light as it passes through a clear (nonabsorbing) solvent containing a dissolved solute that absorbs light at the wavelength being used is proportional to the product of the concentration of solute, the path length, and the extinction coefficient (a factor related to the solute and the wavelength of light).

The Beer-Lambert law can be used rigorously in a laboratory CO-oximeter (which measures the relative concentrations of hemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin) because the exact light path length is known (the diameter of the sample cuvette), the hemoglobin species are in free solution (the erythrocytes are lysed before measurement), and other components of the measuring system have minimal absorption at the wavelengths of light being used. In practice, the manufacturer selects wavelengths of light at which the different hemoglobin species absorb differently, allowing the determination of the concentrations of the individual species (Figure 1). The CO-oximeter is able to report results as the percentage of total hemoglobin; that is, each hemoglobin species, such as oxyhemoglobin, is reported as a fraction of all hemoglobin present.

For the direct measurement of hemoglobin oxygen saturation in vivo, spectrophotometric oximeters designed to mimic laboratory oximeters were developed. The absorption of light through a lobe or pinna of the ear could be measured, but these devices had several problems. First, each patient has variable skin and tissue absorption of light that must be corrected for. The light path length through the body will vary as well because of patient size. Third, the hemoglobin is encased in erythrocytes and is not free in solution. Fourth, because arterial blood oxygen saturation is of primary interest, the presence of desaturated venous and capillary blood had to be taken into account. These difficulties encouraged the development of the pulse oximeter, which uses a different approach to address these problems. Although the basic principles of a spectrophotometer are used, the pulse oximeter incorporates the beat-to-beat change in light absorption to determine oxyhemoglobin.

The pulse oximeter consists of a probe containing LEDs that emit light at fixed, selected wavelengths and a photodetector that measures the amount of this light transmitted through a selected vascular bed (fingertip or earlobe). The derivation of the formula used for pulse oximetry determination of oxyhemoglobin is beyond the scope of this presentation, but the method can be conceptualized as using the variable light-absorbing path length between a peak (at the

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ABBREVIATIONS USED IN TEXT

ET_{CO_2} = end-tidal carbon dioxide pressure
ICU = intensive care unit
LED = light-emitting diode
P_{AO_2} = alveolar partial pressure of oxygen
$P_{\bar{v}CO_2}$ = venous partial pressure of carbon dioxide
$\dot{V}/\dot{Q}$ = ventilation/perfusion

peak of the arterial pulse) and a nadir (the nadir of the arterial pulse, Figure 2). It can be shown that this small variable change in light absorption (compared to the total light absorbed by all of the other tissue, venous blood, skin, and other components) allows relative oxyhemoglobin and hemoglobin concentrations to be determined without knowledge of incident light intensity. Furthermore, it is assumed that all of this change in light absorption is due to arterial blood, so that the pulse oximeter reading will reflect oxygen saturation of arterial blood rather than of venous or capillary blood.

Because of the difference in methodology, the pulse oximeter should not be considered to report the same value as the CO-oximeter would yield for oxyhemoglobin. That is, the CO-oximeter reports oxyhemoglobin as a percentage of total hemoglobin, including methemoglobin and carboxyhemoglobin, while the pulse oximeter gives an estimate of oxyhemoglobin as a percentage of the sum of oxyhemoglobin and deoxyhemoglobin, the "functional oxyhemoglobin" saturation. This can be regarded as the percentage of available hemoglobin that is oxyhemoglobin.

The formulas used in pulse oximetry are rigorous up to a certain point, yet all pulse oximeters have required empirically derived algorithms for practical use. First, although incident light intensity need not be measured for calculation, the pulse oximeter assumes that all light absorbed by the vascular bed was absorbed by the particular hemoglobin species. Because hemoglobin is contained in erythrocytes, some of the light may be scattered away from the photodetector rather than absorbed by hemoglobin. Second, the LEDs are not strictly monochromatic and may be broader in their emitted light wavelength. Because the photodetectors do not discriminate between wavelengths, this may cause a variable and unpredictable effect. In addition, individual LEDs may vary in their central wavelength, a problem that cannot be easily solved even with empiric calibration.[6] Finally, the assumption that all light passes through identical path lengths and homogeneous tissue cannot be accurate.

Although some of these potential problems can probably be minimized by extensive signal processing, results acceptable to manufacturers and users have evolved from empiric calibration on human subjects. Thus, pulse oximeter designs are calibrated by the actual measurement of arterial blood oxygen saturation in volunteer human subjects, and these data are used to derive algorithms that yield acceptable results. The effect of selection bias in the volunteer population has not been rigorously analyzed; however, the unlikelihood of inducing severe arterial hypoxia in normal subjects during pulse oximeter development and calibration may play a role in the apparent inaccuracy of some pulse oximeters when used at low oxygen saturation.[7] Finally, extrapolating data from resting, healthy volunteer subjects to other clinical situations, including exercise testing and critical illness, may not always be possible.

In contrast to the previously described assumptions, which can be dealt with by empiric calibration methods, there are other potentially important artifacts that may arise with the use of pulse oximeters. Movement artifact, a particular problem in exercise laboratories,[8] may also adversely affect accuracy in ICUs. Movement interferes with the pulse oximeter's ability to detect the small pulsatile variation of light absorption. Extraneous incident light, especially if pulsatile or of varying intensity, may fall on the photodetector and result in false readings. Most pulse oximeters sample incident light when the LEDs are turned off to adjust for incident light. This method will not always be successful, however, if the extraneous light source fluctuates in intensity.

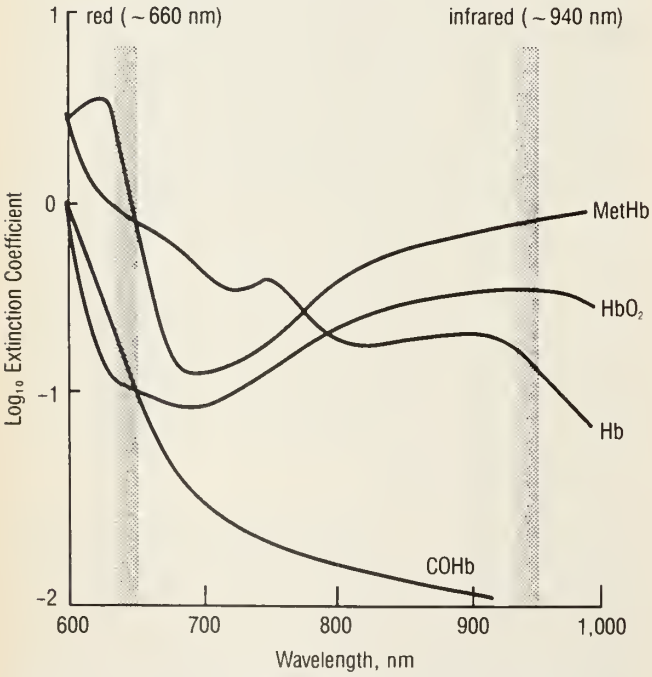

Figure 1.—Absorption spectra are shown (as log extinction coefficients) for hemoglobin (deoxyhemoglobin [Hb]), oxyhemoglobin (HbO_2), methemoglobin (MetHb), and carboxyhemoglobin (COHb) in the range of light wavelengths between 600 and 1,000 nm. The appropriate wavelengths for monochromatic light-emitting diodes (LEDs) used for pulse oximetry are shown for the red LED (660 nm) and for infrared sources (940 nm).

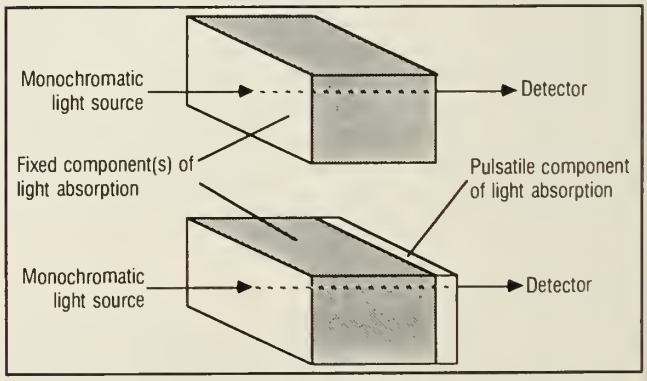

Figure 2.—The conceptual basis for pulse oximetry is depicted. Monochromatic red and infrared light sources transmit light through tissue to a photodetector on the opposite side. The peak-to-nadir difference in light absorption reflects the additional light path length due to the pulsatile addition of arterial blood to the tissue being measured. The method assumes that any pulsatile changes in light absorption detected by the photodetector are due to arterial pulsation. From these data, the relative oxyhemoglobin fraction in arterial blood can be estimated.

TABLE 1.—*Pulse Oximetry in the Intensive Care Unit*

Advantages
Noninvasive
Real time
Continuous
Unobtrusive
Disadvantages
Measures saturation, not P_{O_2}
Movement artifact
Potential Limitations in Intensive Care Unit
Variable performance during hypotension, poor perfusion, use of vasoactive drugs, hypothermia, or carboxyhemoglobinemia
Inaccurate during severe hypoxemia (?)

Pulse Oximetry in Critical Care

There are many advantages to using pulse oximetry in the ICU (Table 1). The procedure is noninvasive and unobtrusive. A substantial number of critically ill patients have hypoxemic respiratory failure, and adjustments of inspired supplemental oxygen concentration, positive end-expiratory pressure, and other respiratory support may benefit from minute-to-minute assessment of oxygen saturation. Weaning from mechanical ventilation and other procedures, such as upper gastrointestinal endoscopy, hemodialysis, and fiberoptic bronchoscopy, can be monitored effectively. The ICU, however, presents unique problems that challenge the pulse oximeter. First, it should be remembered that the pulse oximeter is unable to assess the efficiency of oxygen transfer across the lungs when the P_{aO_2} is high enough to place O_2 saturation on the horizontal part of the oxyhemoglobin dissociation curve. Arterial P_{O_2} and the difference between arterial P_{O_2} and calculated alveolar P_{O_2} ($P_{AO_2} - P_{aO_2}$) are the classic tools used for this assessment. Second, perfusion of the tissue to which the pulse oximeter is attached may be variable in patients in ICUs under conditions of hypotension or shock. Next, intensive care units, as well as emergency departments, occasionally monitor patients with substantially elevated levels of carboxyhemoglobin, and the pulse oximeter does not measure O_2 saturation accurately in the presence of carboxyhemoglobin. Finally, the pulse oximeter may be inaccurate when the arterial oxygen saturation is low and may give misleadingly high values in a patient with dangerous hypoxemia. We will review data on pulse oximetry in some of the conditions commonly encountered in ICUs and in noninvasive monitoring facilities.

The accuracy of pulse oximetry in hypoxemic patients will be considered first. Tremper and Barker recently reviewed available data on pulse oximeter accuracy, including an analysis of five studies in adult volunteers and three studies in adult patients.[6] Overall accuracy, when compared with arterial blood gas determinations, appeared to be excellent in studies that included data spanning the range from normal to below-normal oxygen levels. Because most data collected were in the normal or mildly hypoxic range, however, systematic errors at very low oxygen saturations may have been masked.

In 1986, Chapman and colleagues reported on one model of an oximeter that functioned well during short periods of isocapneic hypoxia in normal subjects when arterial oxygen saturation was greater than 75%.[9] Good correlation ($r = 0.96$) and a small mean difference between oximeter readings and CO-oximeter–determined saturations (0.09%) were noted. When the arterial O_2 saturation was less than 75%, however, the differences were larger (11.2% when O_2 saturations were between 50% and 60%). In a more recent study of volunteers breathing hypoxic gas mixtures,[10] oxygen saturations reported by two pulse oximeter models were accurate when compared with the sum of the percentages of oxyhemoglobin, methemoglobin, and carboxyhemoglobin measured by a CO-oximeter (mean difference of −2.6% and −1.0% between values for each model) over the whole range of 65% to 100% saturation. These models were less satisfactory, however, when the O_2 saturation was between 65% and 80%; there, the mean differences were −4.9% and +3.0%.

Severinghaus and Naifeh used six different oximeters in their study of short-term transient hypoxia in healthy adults.[7] The authors hypothesized that the short duration of the hypoxic transients would be particularly challenging to the different devices, although they thought that there would be sufficient time (30 to 45 seconds) for the pulse oximeters to obtain enough data to calculate a result. During hypoxia with an average arterial oxyhemoglobin reading of 55.5% before termination of hypoxia, mean differences between pulse oximeter and arterial blood oxyhemoglobin readings ranged between −9.0% and 12.0%. There were also important differences between finger probes and ear probes in response time and accuracy. The authors concluded that non-steady state hypoxia of this degree was useful in assessing pulse oximeters and of possible value in calibration procedures and the development of computational algorithms. Because of differences in the data collection and calculation used by the different models, however, it is difficult to determine from this study how much systematic bias exists within or between pulse oximeters during severe hypoxia.

Intensive care unit patients frequently have hypotension, poor tissue perfusion, and impaired oxygen delivery, often combined with the need for vasopressors or vasodilators. Blood flow to the tissues monitored by a pulse oximeter, therefore, may vary, and pulse oximeter O_2 saturations may not necessarily parallel the saturation obtained by a CO-oximeter measuring arterial blood. Of additional importance, pulse oximetry measurements depend on small beat-to-beat differences in light absorption, and decreased pulsatility of the vascular bed during tachycardia, low cardiac stroke volume, or local or systemic abnormalities of the vascular bed may cause additional inaccuracy. Each manufacturer designs into its pulse oximeter computer programs limits of acceptable beat-to-beat variation in light absorption that would preclude reporting a measurement of oxygen saturation. In addition, some recommend that a displayed waveform representing pulsatile light absorption be examined to determine the confidence in the result; however, the exact shape and size of an acceptable waveform has not been rigorously analyzed.

There are remarkably few studies describing the use and limitations of pulse oximeters in ICU patients. For example, Mimh and Halperin concluded that the pulse oximeter was useful in 18 patients with respiratory failure or during weaning from mechanical ventilator support.[11] The device they used did detect clinically significant desaturation in some patients. They also found, however, that their pulse oximeter gave no reading (programmed signal failure) in four patients, none of whom were hypotensive or hypothermic. One patient had peripheral vascular disease; two were receiving do-

pamine or epinephrine. Of interest, other patients who were receiving vasopressors or who had hypotension had signals acceptable to that pulse oximeter. Tremper and associates compared pulse oximeter oxygen saturation measurements with arterial blood O_2 saturation in 53 critically ill patients.[12] Of 383 pairs of data, 53 could not be compared because of pulse oximetry failure due to reported "low perfusion." In the remaining pairs of data, there was overall fair correlation and satisfactorily low variability. In a small subgroup of patients with low O_2 saturation and a discrepancy between pulse oximeter and arterial O_2 saturation, however, systemic vascular resistance was noted to be abnormally high. The authors thought that this effect of high systemic vascular resistance on pulsatility was predictable. They concluded, however, that pulse oximeters were sufficiently accurate over a wide range of hemodynamic conditions in these patients.

In 1989, Pälve and Vuori presented data on limitations of pulse oximetry in patients undergoing cardiac surgical procedures.[13] Two different pulse oximeters were observed for acceptable values of oxygen saturation in 15 patients having open-heart surgical procedures who had hypothermia and low cardiac outputs. Although the authors were interested primarily in the minimum values of cardiac index, finger temperature, and systemic vascular resistance at which the oximeters still functioned, their data showed that low finger temperature (mean of 26°C) and low cardiac index (mean of 2.4 liters per minute) limit accurate measurements. It should be noted that all patients had both conditions and that an interaction between low cardiac index and hypothermia was possible. Gabrielczyk and Buist evaluated pulse oximetry in patients with postoperative hypothermia and found only a small overestimation of O_2 saturation when compared with in vitro measurements.[14]

Several investigators have studied the relationships of blood flow, pulse waveform, and blood pressure to the functioning of available pulse oximeters. In normal volunteer subjects, pulse oximeters continued to provide readings at remarkably low blood flows as estimated by a Doppler flow detector.[15] With increasing pressure in an occluding arm cuff, the pulse oximeter gave an error indication and stopped displaying oxygen saturation only when the cuff was inflated to a pressure of greater than 107 mm of mercury, with a resultant blood flow estimated at only 8.6% of the original inflow. It was concluded that a functioning pulse oximeter should not necessarily be assumed to indicate adequate tissue oxygenation because the data suggest that little arterial blood flow is needed for the instrument and its computer program to calculate a result. In another study, finger-probe O_2 saturation values varied with the position of the hand relative to the heart.[16] The authors thought that this demonstrated an effect of venous pulsations on the pulse oximeter rather than of pulsations limited to the arterial bed. They also speculated that the increased influence of venous blood in the pulsatile component of light absorption would lead to inaccurate readings, especially with low arterial pulse pressure and decreased mean arterial blood pressure. Interestingly, no difference was found in mean pulse oximeter saturation when finger-probe readings were compared between hands with and without radial artery catheters.[17] Hypotension, vascular disease, or other conditions, however, might make an additional difference.

Severinghaus and Spellman recently reported on an analysis of several pulse oximeters' responses to decreased perfusion induced by several methods designed to separate the effects of hypotension, hypoperfusion, and decreased pulsatility.[18] When the brachial artery was progressively occluded in normal subjects, the pulse oximeters failed to report O_2 saturation only when the ipsilateral radial artery pressure fell below 36 to 47 mm of mercury. When the subjects' arms were elevated and hypotension was induced by nitroprusside administration, the mean pressure at which the pulse oximeters stopped reporting results was approximately 30 mm of mercury. The authors concluded that brachial artery occlusion decreased both mean perfusion pressure to the finger and beat-to-beat light absorption at the finger probe. The nitroprusside-induced hypotension, on the other hand, decreased mean perfusion pressure but maintained pulsatility. The authors pointed out that the pulse oximeters still were functional under conditions of severely reduced distal extremity blood flow. Furthermore, arterial hypoxia induced during arm elevation and hypotension were not detected by the pulse oximeter in one test for six minutes. The authors concluded that pulse oximeters may assume acceptable pulsatility when blood pressure is too low to provide adequate tissue blood flow. Thus, tissue oxygen consumption may result in a misleadingly lowered pulse oximeter O_2 saturation reading. Finally, there appears to be an interaction between systolic pressure and pulse pressure that determines the minimum arterial pressure at which pulse oximeters fail.

Carbon monoxide toxicity is treated infrequently in intensive care units but may be seen in emergency departments. Pulse oximeters can neither measure carboxyhemoglobin nor accurately determine oxyhemoglobin in its presence. While it is sometimes claimed that this is because there are only two wavelengths of light used in commercially available pulse oximeters,[5] this explains only why pulse oximeters cannot measure carboxyhemoglobin. The error in oxyhemoglobin detection is because oxyhemoglobin, reduced hemoglobin, and carboxyhemoglobin do not differ sufficiently in their absorbance characteristics at the red and infrared wavelengths used.[6] Severinghaus proposed that pulse oximeters can accurately report reduced (deoxygenated) hemoglobin in the presence of carboxyhemoglobin.[19] That is, the oxygen saturation displayed is essentially equal to 1-deoxyhemoglobin, but the relative concentrations of oxyhemoglobin and carboxyhemoglobin are unknown. In dogs, the calculated pulse oximeter saturation was found to be empirically equal to oxyhemoglobin + (0.9 × carboxyhemoglobin) as a percentage of the total hemoglobin.[6,20] The pulse oximeter will not measure oxyhemoglobin accurately in the presence of carboxyhemoglobin and, in fact, will give misleadingly high estimates of the adequacy of oxygenation of the arterial blood. In ICU patients, other colored substances in the blood could affect light absorbance at relevant wavelengths. These include bilirubin, which has little important effect on pulse oximetry[21,22]; methemoglobin, generated in the presence of oxidizing agents such as nitrites and sulfonamides, which increases the difference between functional O_2 saturation as measured by the pulse oximeter and oxyhemoglobin measured by the CO-oximeter at low concentrations, and has the peculiar effect of causing the pulse oximeter always to read 85% when present in high concentrations[6]; and a variety of dyes occasionally used to measure cardiac output, such as indocyanine green.

In summary, the pulse oximeter uses a unique combination of a pulse plethysmograph and a spectrophotometer to

provide a noninvasive means of estimating arterial blood oxygen saturation. Several important assumptions are made in adapting the use of pulse oximetry for clinical purposes, and all devices by necessity use empiric calibration. The clinical conditions of patients in ICUs further challenge pulse oximeters to function accurately, including severe hypoxemia, abnormally low blood flow, hypotension, and the possible presence of carboxyhemoglobin. Nevertheless, studies indicate that most clinical patients have remarkably close agreement between pulse oximeter estimates of arterial oxygen saturation and simultaneous arterial blood oxyhemoglobin concentration, largely because most of these patients have oxygen saturations above 75% and are not hypotensive. In patients with severe hypoxemia or poor tissue perfusion, however, the effectiveness and accuracy of pulse oximetry may vary, and the results should be used with caution. Further study may be needed to discriminate between clinical conditions in ICUs that can and cannot yield accurate results with a particular pulse oximeter. Finally, although pulse oximetry has become widespread and perhaps even a standard of care, studies documenting the actual effect of pulse oximetry on the quality of patient care are lacking.

Principles of Capnography

Carbon dioxide is the second respiratory gas of interest in critical care patients. Until recently, carbon dioxide was measured clinically only by routine arterial blood gas determinations. An examination of expired CO_2 permits a continuous noninvasive measurement of alveolar P_{CO_2} and an estimation of arterial P_{CO_2}.[23,24] The proper use and interpretation of this technique, termed capnography, requires a basic understanding of the physiology of carbon dioxide production, transport, and elimination. We shall address each of these in turn, paying particular attention to their effects on expired CO_2 measurement.

Carbon dioxide is a major product of metabolizing tissue and, as such, must be transported and eliminated. Diffusion carries carbon dioxide away from its cellular site of production to the capillary interface where it enters the blood. The efficiency of transport is a function of the rate of blood flow and its carrying capacity. Most carbon dioxide (60% to 70%) is transported as dissolved carbonic acid.[25,26]

The arteriovenous CO_2 difference in normal persons is approximately 6 mm of mercury ($P_{aCO_2} = 40$ mm of mercury, $P_{\bar{v}CO_2} = 46$ mm of mercury) and is eliminated by the lungs. Expired CO_2 can be measured in several ways. If exhaled gas is collected over time in a large reservoir, mixed expired CO_2 will be measured. Breath-to-breath variations will not be reflected, nor will short-term changes in carbon dioxide production or elimination. The average concentration in normal persons for the CO_2 thus obtained is about 3.5%. This concentration of carbon dioxide may be converted to a partial pressure term by using the equation:

$$P_{CO_2} \text{ (mm of mercury)} = (P_B - P_{H_2O}) \times \% \ CO_2$$

where P_B is the barometric pressure (about 760 mm of mercury) and P_{H_2O} is the vapor pressure of water (about 47 mm of mercury).

The successful application of capnometry requires an appreciation of the expired CO_2 waveform and the factors that influence it. If the concentration of carbon dioxide in exhaled gas is plotted against time, a characteristic waveform (Figure 3) will be obtained that has four distinct parts. The first portion, or baseline, is obtained between breaths when there is no active gas flow and at the start of exhalation when carbon dioxide-free gas from anatomic dead space (such as the trachea) is exhaled. The ascending or second portion occurs when alveolar gas begins to mix with gas from carbon dioxide-poor dead space. As more and more alveoli empty, the carbon dioxide concentration rises rapidly until the alveolar plateau is reached. This plateau represents the contribution from both actively exchanging, "ideal" lung units and nonexchanging, underperfused alveoli. The point at which the plateau turns downward at the end of exhalation is called the end-tidal point; the concentration measured at that moment is the end-tidal CO_2 concentration (ET_{CO_2}). As inhalation begins in segment 4, fresh carbon dioxide-free gas passes the detector, causing the carbon dioxide concentration to fall rapidly to near zero. An elevation of the baseline is indicative of residual carbon dioxide and may be due to a malfunctioning expiratory valve in a mechanical ventilator, allowing the rebreathing of carbon dioxide, or to an exhausted CO_2 absorber in an anesthesia circuit.

Under normal circumstances, the ET_{CO_2} is a good approximation of P_{aCO_2}. Various mechanical and patient-related factors, however, can adversely influence the result. Among physiologic factors, alterations in ventilation-perfusion ($\dot{V}/\dot{Q}$) relationships are the most significant. The most important $\dot{V}/\dot{Q}$ abnormality affecting capnography is dead space ventilation. In simple terms, dead space consists of that portion of the tidal volume that does not contribute to gas exchange. Physiologic dead space is defined as the sum of apparatus dead space, anatomic dead space, and alveolar dead space.[27,28]

Apparatus and anatomic dead spaces are the most straightforward of the three types. The apparatus dead space is that part of the respiratory circuit that contains delivered gas—primarily the endotracheal tube, with minor contributions from connectors. The apparatus dead space is usually constant and exerts its effect by prolonging phase I of the capnograph. The anatomic dead space is composed primarily of the conducting airways. The rapid upstroke in phase II is caused by gas in the anatomic dead space, which is generally defined as the volume of gas exhaled before the carbon dioxide concentration increases to its alveolar plateau. The volume of anatomic dead space varies and is influenced by such factors as patient size, posture, position of the neck and jaw, age, lung volume at the end of inspiration, drug treatment, and temperature. Apparatus and anatomic dead spaces are exhaled sequentially and constitute volumes in series. Increases in the series dead space reduce overall minute ven-

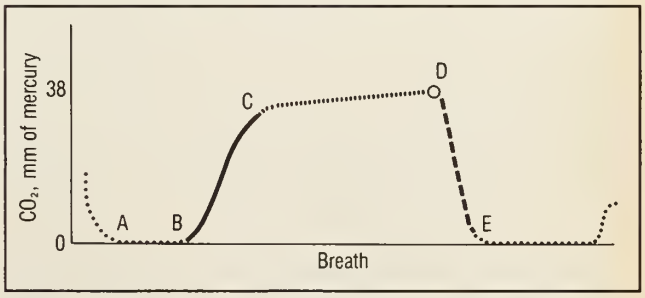

Figure 3.—A normal capnograph consists of four distinct segments, beginning at the zero baseline (A to B), a rapid, sharp rise (B to C), an alveolar plateau (C to D), and a rapid, sharp downstroke (D to E). The point ending the alveolar plateau, just before the start of inhalation, is termed the "end-tidal point" (D).

tilation, thereby causing an increase in both arterial CO_2 and end-tidal CO_2.

The third, and most important, component of physiologic dead space is the alveolar dead space, defined as the fraction of the inspired gas that traverses the apparatus and anatomic dead space to mix with gas in the alveoli but that does not take part in gas exchange. The most common cause of alveolar dead space is inadequate perfusion of the alveoli. Nunn has pointed out that there is an infinite range of $\dot{V}/\dot{Q}$ mismatch throughout the lung, leading to heterogeneous areas of alveolar dead space.[28] Those alveoli with normal $\dot{V}/\dot{Q}$ matching produce "ideal" alveolar gas, while those without any perfusion ($\dot{V}/\dot{Q} = \infty$) constitute true alveolar dead space. The overall $\dot{V}/\dot{Q}$ ratio in a healthy person is a weighted average of these areas and has been estimated to be near 0.8.[29(p64)] Alveoli are emptied essentially simultaneously, rather than sequentially, and gas from the different units combines in parallel, rather than in series. This parallel alveolar dead space may be influenced by hypotension or by a loss of alveolar perfusion due to pulmonary embolism, pulmonary artery hypertension, and posture. In the decubitus position, about two thirds of the cardiac output perfuses the dependent side, and when breathing is spontaneous, ventilation follows perfusion resulting in minimal dead space. When positive pressure ventilation is used, however, most of the tidal volume is distributed to the upper lung and alveolar dead space increases.[28]

The capnographic alveolar plateau represents a mixture of exhaled parallel alveolar gas components. As alveolar dead space increases, the alveolar plateau (and $ETco_2$) falls, even though the $Paco_2$ increases. This results in a widened arterial–end-tidal gradient, with an underestimation of the arterial Pco_2 by the $ETco_2$. Increased arterial Pco_2 stimulates chemoreceptors, resulting in a return to a normal $Paco_2$ (if the lungs are not extremely diseased), but further lowers the mixed expired CO_2. Again, the arterial–end-tidal gradient is increased. In essence, the size of this gradient may be thought of as an indirect measure of the alveolar dead space.

The other major contributor to $\dot{V}/\dot{Q}$ mismatch is shunt, in which well-perfused alveoli receive no ventilation ($\dot{V}/\dot{Q} = 0$). Because these alveoli do not receive respiratory gas, they decrease the oxygenation of the blood more than they affect either the $ETco_2$ or $Paco_2$. If the mixed venous Pco_2 is 46 mm of mercury, but the $Paco_2$ is normal at 40 mm of mercury, increasing the shunt to 50% would increase the $Paco_2$ to only 43 mm of mercury while decreasing the $ETco_2$ minimally.[27] This is true not only because the venoarterial change in Pco_2 is small, but also because the dissociation curve for CO_2 is linear in this region.[27,28] Liu and co-workers have recently demonstrated clinically that shunt contributes only a small amount to the arterial–end-tidal gradient (S. Y. Liu and F. S. Bongard, "Capnometry Accurately Estimates Arterial CO_2 in Nonintubated Patients," unpublished data, September 1991). Conversely, Yamanaka and Sue have shown a strong correlation between the arterial–end-tidal gradient and dead space in a group of intubated and ventilated patients with primary respiratory disease.[30]

Either of two techniques may be used to determine the concentration of carbon dioxide in exhaled gas: infrared absorption or mass spectrometry. Mass spectrometers usually have a rapid response time (less than 100 milliseconds) and can analyze several gases simultaneously. The instruments are large, expensive, and require frequent maintenance. Because of these limitations, they are usually used on a shared basis in surgeries or research laboratories. Infrared spectrometry has become popular in recent years following the development of light-emitting diodes that are inexpensive, monochromatic, and energy efficient. In infrared spectrometry, a specimen of gas is passed between two infrared light beams. Carbon dioxide molecules absorb part of the available light, thus decreasing its intensity in direct proportion to the concentration of gas present. The response time of an infrared absorption capnometer is somewhat slower than that of a spectrophotometer, but the instrument is smaller, far less expensive, and easier to transport. Because the absorption spectrum of nitrous oxide is close to that of carbon dioxide, most instruments offer simultaneous measurement and display of both gases.

The optical sensor may be placed in line with the patient's breathing circuit (in-line system), or gas may reach it through a small adapter hooked to the circuit near the endotracheal tube (side-stream system). The disadvantage of an in-line system is that the optics and associated electronics ("optical bench") may be excessively heavy for awake patients and constitute a possible ventilator disconnect hazard. Side-stream systems require that a sampling tube be connected to the remote optics at the bedside. Gas is aspirated from a point in the respiratory circuit close to the endotracheal tube. For nonintubated patients, a modified nasopharyngeal airway or nasal cannula may be used (F. S. Bongard, Y. Wu, M. Lippmann, and T. S. Lee, "Accuracy of Capnography in Nonintubated Postoperative Patients," unpublished data, December 1990). The typical sampling rate for a side-stream system is between 50 and 100 ml of exhaled gas per minute. Anything that interferes with the delivery of sampled gas to the optics will adversely affect the accuracy of the expired CO_2 measurement. This is particularly problematic in side-stream systems where the sampling catheter may become obstructed with secretions or bent by another apparatus. When this occurs, the displayed waveform becomes dampened and the displayed $ETco_2$ drops rapidly. Failure to examine the waveform and diagnose the cause of the decreased $ETco_2$ may lead to erroneous conclusions about a patient's respiratory status. Insufficient sampling rates will delay information and disperse gas in the sampling tube, which results in a distorted waveform.[27] If the flow rate is too high, room air or supplemental oxygen can be entrained through the sampling cannula. Because the expired gas contains water vapor at the patient's body temperature, condensation in the sampling tube and at the optical detector are potential problems. Water traps, semipermeable tubing, and filters have been used to alleviate this difficulty, with varying degrees of success.[27] If water enters the actual detector, its infrared absorption will produce false readings. Because mainstream systems are exposed to the direct humidified respiratory circuit, they are usually heated (40°C) to prevent condensation on the detector optics.

Clinical Applications of Capnography

In patients with regular respiration and stable cardiac hemodynamics, trends in the $ETco_2$ are useful for evaluating the ventilatory status.[31] It must be noted at the outset, however, that a change in $ETco_2$ does not necessarily indicate an altered $Paco_2$. For example, a patient with respiratory distress who is being mechanically ventilated may have an $ETco_2$ of 36 mm of mercury while his $Paco_2$ is 43 mm of

TABLE 2.—*Advantages and Limitations of Capnography*

Advantages	Disadvantages
Continuous	Affected by increased alveolar dead space
Noninvasive	Least accurate in sickest patients
Displays CO_2 waveform	Depends on patency of sampling system
Analyzes inspired CO_2	Change in $ETco_2$ does not necessarily reflect extent or direction of change in $Paco_2$
Rapid response time	
Usable in intubated and nonintubated patients (side stream only)	

$ETco_2$ = end-tidal carbon dioxide

mercury. This widened arterial–end-tidal CO_2 gradient is consistent with the increased $\dot{V}/\dot{Q}$ mismatch that accompanies the respiratory distress syndrome. An increase in the $ETco_2$ from 36 to 40 mm of mercury may be explained by several mechanisms: worsening hypercarbia with increased peripheral carbon dioxide production and no change in the $\dot{V}/\dot{Q}$ ratio (or arterial–end-tidal CO_2 gradient), an improved alveolar $\dot{V}/\dot{Q}$ ratio with $ETco_2$ more closely approximating the alveolar CO_2, or a combination of the two. If the dead space and shunt are relatively constant, trends in the $Paco_2$ can be detected with capnography.

Recalling that alterations in the capnographic waveform and changes in the arterial–end-tidal CO_2 gradient may be due to carbon dioxide production (metabolism), carbon dioxide delivery (circulation), or elimination (alveolar ventilation), the applications and shortcomings of capnography in critical care can be detailed (Table 2). The technique is useful for tracking carbon dioxide in both intubated and nonintubated patients (S. Y. Liu and F. S. Bongard, unpublished data, September 1991). It is an immediate indicator of ventilator circuit disconnection or apnea. Other causes of rapid decreases in the $ETco_2$ include complete airway or circuit obstruction, dislodgement of the endotracheal tube into the esophagus or esophageal intubation, sudden hypotension or hemorrhage, circulatory arrest, and pulmonary embolism. Increased $ETco_2$ may be caused by increased carbon dioxide production (such as hypermetabolism, hyperthermia, or hyperalimentation), absorption of carbon dioxide from exogenous sources (laparoscopy with carbon dioxide), and partial airway obstruction. Alterations in the shape of the waveform may be due to alveolar hypoventilation. A typical scenario occurs in a tachypneic patient with decreased tidal volume. Residual carbon dioxide-rich alveolar gas remains after the completion of exhalation, and the $ETco_2$ never reaches a maximum value reflective of arterial CO_2. Again, examination of the capnograph fails to reveal a waveform with an alveolar plateau or a clear end-tidal point. The arterial–end-tidal CO_2 gradient will be widened with an artificially depressed $ETco_2$.

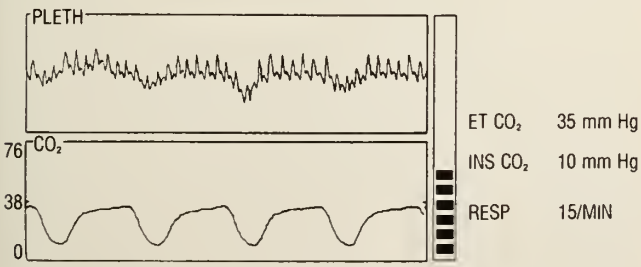

Figure 4.—The capnograph shows a failure of the baseline to return to zero. The inspired CO_2 (INS CO_2) was 10 mm of mercury. The cause was a malfunctioning ventilator valve. ET CO_2 = end-tidal carbon dioxide, PLETH = plethysmograph, RESP = respiratory rate

Case Studies

Two case reports will help illustrate the use of capnography in critical care.

Case 1. The first patient, a 42-year-old woman, underwent laparotomy for a low sigmoid carcinoma. Eighteen hours postoperatively she was hemodynamically stable on a mechanical ventilator. Blood gas measurements indicated a pH of 7.28 and $Paco_2$ of 46 mm of mercury. Minute ventilation was increased with no change in the arterial Pco_2. End-tidal CO_2 was 35 mm of mercury. The capnographic tracing is shown in Figure 4. Note that the baseline segment does not reach zero. Inspired CO_2 is 10 mm of mercury. Evaluating the blood gases and the capnometric data indicated that the increased minute ventilation failed to decrease the arterial Pco_2 because the patient was rebreathing exhaled gas rich in carbon dioxide. An examination of the ventilator found a malfunctioning valve, permitting the patient to exhale into the inspiratory reservoir. When the ventilator was exchanged for a functioning one, the $Paco_2$ quickly fell to within normal limits.

This case shows that capnography is a useful adjunct to arterial blood gas determinations. Without the capnographic waveform and confirmation of an elevated inhaled CO_2 level, the diagnosis of the cause of this patient's hypercarbia would have been prolonged. The information supplied by the capnograph permitted a rapid evaluation of the cause of the problem.

Case 2. The patient, a 22-year-old man, sustained six left rib fractures in a motor vehicle accident. On admission to an intermediate care unit, he was noted to be in mild respiratory distress with shallow inspirations at a rate of 30 per minute. Arterial blood gas determinations revealed a $Paco_2$ of 36 mm of mercury, with an $ETco_2$ of 33 mm of mercury obtained by nasal cannula. Over the next several hours, he received small doses of narcotic analgesia with an increase in the $ETco_2$ to 45 mm of mercury. Intercostal rib blocks were performed. His respiratory rate decreased with a rise in the tidal volume and a fall in the $ETco_2$ to 37 mm of mercury. Over the next few days, rib blocks were repeated and his CO_2 monitored by capnography. The patient never required endotracheal intubation and hence was cared for in a noninvasive transitional care unit.

This case illustrates the use of capnography in nonintubated critical care patients. Once the arterial–end-tidal CO_2 gradient is established, the $ETco_2$ can be used effectively to monitor ventilation as long as the dead space does not change appreciably. Repeat blood gas determinations were obviated in this patient with their associated discomfort and cost. Other instances where $ETco_2$ monitoring in nonintubated patients has proved useful are after extubation, when monitoring patients after thoracostomy or needle aspiration, in patients receiving narcotic analgesia, in patients with multiple trauma, and in patients with simple sepsis.

Conclusion

Pulse oximetry and capnography offer two useful noninvasive techniques to facilitate respiratory monitoring in critical and transitional care units. An understanding of underlying assumptions and limitations can greatly aid in patient monitoring. Their judicious use can reduce the number

of invasive blood gas determinations required and lead to reduced costs and increased patient safety.

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Epitomes

Important Advances in Clinical Medicine

Internal Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in internal medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Ventilator Management of Severe Asthma

ACUTE, SEVERE, POTENTIALLY life-threatening asthma is recognized to have several features that stress the predominance of bronchial mucosal inflammation and edema and debris in the airway lumen, in conjunction with bronchial smooth muscle contraction, as the causes of airway obstruction. One important clinical consequence is that the increasingly severe airway obstruction may show marked diurnal fluctuation. Other features, results of the predominance of airway inflammation compared with bronchospasm, include prolonged severe bronchial lumen narrowing once established, refractoriness to bronchodilators, and the need for therapy that addresses the inflammatory component.

When acute severe asthma develops, the mainstays of therapy are corticosteroids plus bronchodilators, including inhaled β-adrenergic agonists, and, to a lesser extent, theophylline and ipratropium bromide. The beneficial effect of corticosteroids requires at least several hours.

The slow response of airway inflammation to pharmacologic treatment means that even with aggressive medical therapy, respiratory failure requiring mechanical ventilation develops in some asthmatic patients. Because of the greatly increased work of breathing due to increased airway resistance, these patients cannot maintain sufficient ventilation to compensate for increased ventilation-perfusion mismatching. Mechanical ventilation, however, has been associated with especially high mortality rates in asthmatic patients (22% in one recent series), and serious complications of barotrauma and impaired cardiovascular function are not infrequent.

Recent studies have emphasized the likelihood of hyperinflation in asthmatic patients who are mechanically ventilated. The narrowed airways in asthmatic patients have a more pronounced effect on expiratory than on inspiratory resistance; this is true whether patients are spontaneously breathing or mechanically ventilated. If there is insufficient time for exhalation, air trapping or hyperinflation may result. Hyperinflation has a major effect on gas exchange, especially increasing the physiologic dead space, and may result in tidal ventilation at a less compliant portion of the respiratory system pressure-volume curve. Thus, asthmatic patients in whom hyperinflation develops during mechanical ventilation may have worsening of gas exchange and require dangerously high airway pressures.

New strategies for mechanical ventilation in patients with acute asthma emphasize the use of high inspiratory flow and slow breathing frequency—the latter sometimes requiring sedation or neuromuscular blockade—to prolong expiratory time and allow end-expiratory lung volume to decrease to more normal levels. An improvement in arterial blood gas values, at times paradoxically in response to decreased minute ventilation, or a fall in peak airway pressure is indicative of decreased hyperinflation. In many patients, hyperinflation may be identified by the presence of "intrinsic positive end-expiratory pressure"—most easily detected by finding positive airway pressure during occlusion of the exhaust port of the ventilator immediately before the next inspiration—and this finding should be used to guide changes in ventilatory settings. The administration of a high inspired concentration of oxygen (40% to 50% of oxygen) may help inhibit hypoxic respiratory drive, slowing the respiratory rate and prolonging the expiratory phase. Some investigators have suggested that some degree of hypercapnia can be accepted as a consequence of limiting airway pressure, tidal volume, or respiratory frequency, rather than using more conventional ventilatory settings intended to provide a patient with sufficient ventilation to maintain normal P_{CO_2} and pH. This "controlled hypoventilation" may result in reduced complications from hyperinflation.

The use of more recently introduced modes of ventilation, such as pressure support and pressure control, has yet to be compared with conventional modes in clinical trials in asthmatic patients. Both of these modes may be used to limit peak airway pressure, but other characteristics may or may not be optimal for use in acute airway obstruction.

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New Trends in Treating Chronic Persistent Asthma in Adults

GUIDELINES FOR THE MANAGEMENT of chronic persistent asthma have recently been published. The impetus for these guidelines was the worldwide increase in morbidity and mortality from asthma, which has been attributed, in part, to the underuse of anti-inflammatory agents, the underuse of objective measurements of asthma severity, and the inadequate education of patients and health care professionals.

The overall aims of management are to recognize asthma and changes in asthma severity, relieve symptoms, restore the best possible long-term lung function, and minimize the risk of a severe attack. Asthma is best controlled by avoidance, if possible, of potentially harmful factors including allergens, occupational chemical sensitizers, viral respiratory tract infection, specific additives to foods, beverages, and drugs (such as bisulfites), certain drugs (such as β-adrenergic antagonists), and cigarette smoke; the treatment of aggravating conditions (such as gastroesophageal reflux or sinusitis); and the use of antiasthma medication in the lowest doses that will achieve maximal control with minimal short- and long-term side effects. The types and doses of medication recommended for the treatment of asthma are tailored to the severity of the disease, as outlined later. An objective monitoring of asthma severity using home measurements of peak expiratory flow is important to guide treatment. Moreover, treatment is more effective when the patient is active in the management of the disease.

Mild asthma is defined as intermittent, brief symptoms two times per week or less. It includes brief symptoms with exercise and no symptoms and normal or nearly normal lung function between episodes. β_2-Agonists should be used as required, preferably by inhalation in doses of one to two puffs from a metered-dose inhaler (MDI) or the equivalent dose from a powder inhaler, every three to four hours as needed, for the relief of acute symptoms of asthma and for the prevention of symptoms caused by exercise or exposure to allergens or other stimuli. Alternatively, cromolyn sodium, one to two puffs from an MDI, may be used for prophylaxis before exposure to provocative stimuli. For patients with mild asthma, this may be the only treatment required. For more symptomatic, newly detected mild asthma, an inhaled corticosteroid administered twice a day was recently found to be an effective first-line treatment and superior to regular dosing with an inhaled β_2-agonist.

Moderate asthma is defined as symptoms occurring more than once or twice a week. Exacerbations can affect sleep and activity level and may last several days. There is an occasional need for emergency care. Lung function is 60% to 80% of expected and varies greater than 30% during the worst exacerbations. In patients with chronic persistent asthma of more than mild severity, regularly scheduled maintenance therapy is required to achieve satisfactory control—defined as minimal symptoms, normal activity tolerance, and optimum lung function. Asthma severity and the need for therapy are thought to be linked to the degree of airway inflammation. Therefore, the primary emphasis for maintenance treatment is now placed on anti-inflammatory therapy, especially the use of inhaled corticosteroids, supplemented, if necessary, by short courses of oral corticosteroids. In patients with moderate to severe asthma, the currently recommended practice is to prescribe inhaled corticosteroids (three to four puffs twice a day initially) or cromolyn (two puffs four times a day), together with inhaled β-agonists, as needed.

If symptoms persist and the frequency of as-needed use of inhaled β-agonists exceeds three to four times a day, the dose of inhaled corticosteroids is increased. In addition, a sustained-release theophylline or oral β_2-agonist may be prescribed, especially for the relief of nocturnal symptoms. If symptoms occur with increasing frequency or severity (lung function declines by more than 30%), a short course of oral prednisone or the equivalent should be instituted, followed by higher doses of inhaled corticosteroids.

Severe asthma is defined as continuous symptoms, limited activity tolerance, frequent exacerbations, and nocturnal symptoms. Occasional hospital admissions and emergency treatment may be required. Lung function is less than 60% of predicted, and there is more than 50% variation during the worst exacerbations. Inhaled corticosteroids are prescribed in larger doses—four to six puffs two to four times a day—together with inhaled β_2-agonists, one to two puffs by MDI as needed and two to four puffs, or nebulized treatment, for the worst exacerbations. An oral sustained-release theophylline, oral β_2-agonist, or inhaled anticholinergic (such as ipratropium bromide) may also be added. In addition, oral corticosteroids are usually required in relatively short "bursts" for active symptoms (such as prednisone, 40 mg once a day or in divided doses for a week, then 10 mg once a day for a week).

Some patients with severe asthma may require daily or alternate-day corticosteroids (single morning dose) for the adequate control of symptoms. Unconventional "steroid-sparing" agents—such as low-dose weekly methotrexate, oral or injectable gold salts, or troleandomycin—have been proposed for the treatment of severe, corticosteroid-dependent asthma to achieve better asthma control and reduce the risk of complications of long-term corticosteroid therapy. These unorthodox regimens, while promising, are still experimental, and their benefits and short- and long-term risks remain to be clarified. The aggressive application of current recommendations for asthma therapy should obviate the need for recourse to experimental medication in most patients.

In a recent study, significantly more patients with chronic persistent asthma—most of whom were using inhaled corticosteroids—achieved better control during as-needed-only than during regularly scheduled treatment with an inhaled β_2-agonist (fenoterol, not currently available in the United States). It is not clear whether these results are generalizable to all inhaled bronchodilators or are specific to fenoterol, which is less β_2-specific than albuterol or terbutaline and is generally dispensed in twice the bioequivalent aerosol dose as that of other inhaled β-agonists. Nevertheless, these findings raise serious questions concerning the efficacy and safety of regularly scheduled, as opposed to simply as-needed, inhalations of a β-agonist aerosol that need to be addressed in additional well-designed studies.

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Potent Antiemetic Effects of the New Serotonin Antagonists

PATIENTS CONSISTENTLY rank chemotherapy-induced emesis first among the adverse effects associated with oncologic treatment. Two thirds of the more than 30 effective antineoplastic agents can precipitate moderate to severe nausea and vomiting. Chemotherapy-induced emesis not only affects patients' quality of life but also their general medical condition through electrolyte disturbances, anorexia, cachexia, Mallory-Weiss tears, and aspiration pneumonia. Consequently, patients frequently withdraw from chemotherapy.

Chemotherapy-induced emesis is a complex process with many causes. Assorted afferents stimulate the emetic center located in the lateral reticular formation of the medulla oblongata, which initiates and coordinates the complex somatic and visceral actions of emesis. These triggering afferents include a humoral pathway by the chemoreceptor trigger zone, peripheral pathways in the gastrointestinal tract, and central pathways through the vestibular, limbic, and midbrain systems. Although the neuroanatomy of the emetic process has been recognized for decades, neurohumoral details have been shown only in the past several years. This knowledge provides the means for a more selective and effective prevention of chemotherapy-induced emesis.

The chemoreceptor trigger zone is located in the floor of the fourth ventricle, where it is bathed by blood and cerebrospinal fluid, and contains receptors for dopamine, serotonin, opiates, and histamine. Early antiemetic trials largely employed phenothiazines, butyrophenones, metoclopramide hydrochloride, cannabinoids, and corticosteroids alone or in combination in an attempt to block dopaminergic, presumed higher cortical, and putative peripheral receptors. Results of these trials showed only modest efficacy. More modern regimens using high-dose metoclopramide, usually in combination with dexamethasone and lorazepam, demonstrated greater success. Unfortunately, these regimens are relatively complex, expensive, and frequently associated with unpleasant side effects, including sedation, diarrhea, and extrapyramidal reactions. Subsequent research revealed that the chemoreceptor trigger zone and the vagal afferents in the small bowel are rich in a serotonin-receptor subtype, 5-hydroxytryptamine$_3$ (5-HT$_3$). Because the enterochromaffin cells in the small bowel contain serotonin, it was conjectured that acute emesis less than 24 hours after chemotherapy may in part be due to a chemotherapy-mediated release of serotonin from these enterochromaffin cells. This serotonin may stimulate the 5-HT$_3$ receptors of the chemoreceptor trigger zone and those on afferent vagal fibers, either of which, in turn, could trigger the emetic center.

Intravenously administered ondansetron hydrochloride (Zofran [Glaxo, Inc, Research Triangle Park, NJ]) is the first of several highly selective, competitive 5-HT$_3$ receptor antagonists to receive approval from the US Food and Drug Administration (FDA) for chemotherapy-induced emesis. In Europe both ondansetron and granisetron are available. In published trials involving more than 2,500 patients, ondansetron proved to be superior to previously available antiemetics in the control of acute chemotherapy-induced emesis in both cisplatin- and non–cisplatin-containing regimens. Indeed, ondansetron provides 72% major or complete antiemetic response versus 41% for high-dose metoclopramide in patients receiving cisplatin. This benefit is amplified by ondansetron's highly favorable toxicity profile (mild headaches and rare transient aminotransferase elevations) and its lack of antidopaminergic complications, such as extrapyramidal reactions. An equally effective oral formulation is available in Europe and is pending FDA approval. Like metoclopramide, ondansetron's efficacy is enhanced by adding dexamethasone (complete short-term response greater than 90%), supporting the important but as yet poorly understood role of inflammatory mediators in chemotherapy-induced emesis.

Of note, ondansetron's antiemetic effects are associated primarily with the acute chemotherapy-induced emesis and are distinctly less pronounced with the delayed-phase (more than 24 hours) type. In fact, in delayed emesis, its efficacy is reportedly no better than, and in some series inferior to, that of metoclopramide. Nonetheless, because of its favorable toxicity profile, patients prefer it to metoclopramide even in this setting.

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Recent Advances in Diagnostic Tests for Syncope

SYNCOPE AFFECTS 30% to 50% of the adult population and accounts for about 300,000 emergency department visits each year. Despite an estimated cost of $750 million spent on diagnostic tests for patients admitted to hospital, the cause of syncope remains unknown in more than 40% of patients. A rational approach to the diagnosis and management of syncope is essential.

The history and physical examination remain the most critical part of the initial evaluation of a patient with syncope. Of those patients to whom a diagnosis can be assigned, the history and physical examination identify the cause as much as 85% of the time. Except for the diagnosis of arrhythmias, most other causes of syncope are strongly suggested by the initial history and findings of a physical examination. An initial electrocardiogram or rhythm strip can detect a precipitating arrhythmia in 2% to 11% of patients and cardiac monitoring does so in an additional 3% to 27%. In patients who remain undiagnosed, several different approaches can be used.

While electrophysiologic studies are increasingly used in the workup of patients with syncope, not every person needs or benefits from these invasive and expensive tests. These studies are valuable for assessing life-threatening ventricular tachyarrhythmias and less helpful in determining bradyarrhythmic causes of syncope. The studies have their greatest diagnostic yield in patients with known heart disease manifested by depressed ventricular function or an abnormal electrocardiogram or Holter monitoring.

Signal-averaged electrocardiography is a diagnostic test that helps identify those patients who would benefit from

electrophysiologic studies. This noninvasive technique detects low-amplitude, high-frequency signals at the terminal portion of the QRS complex. In patients with syncope, the presence of these signals appears to have a sensitivity and specificity of 80% to 90% for eliciting serious ventricular arrhythmias by electrophysiologic studies.

Although frequently ordered, ambulatory Holter monitoring may not define an exact cause of syncope because of the lack of well-established criteria for interpreting abnormal results. To determine a specific cause for syncope, the recorded arrhythmia must coincide with the patient's symptoms, but this occurs in only 3% to 5% of cases. Some arrhythmias are common among the general population. For example, bradycardia (less than 40 beats per minute), brief runs of supraventricular tachycardia, premature ventricular contractions, and even multiform or paired premature ventricular contractions have been recorded in substantial percentages of asymptomatic ambulatory patients. The optimal duration of monitoring has also not been determined. Patient-activated intermittent recorders, loop recorders, and transtelephonic electrocardiographic recordings are useful alternatives in patients in whom an arrhythmic cause is strongly suspected.

In patients without known heart disease, the head-up tilt test can be useful in diagnosing vasovagal syncope. This noninvasive procedure involves tilting a patient at 60 to 80 degrees for 10 to 60 minutes with or without an infusion of isoproterenol hydrochloride. A positive response reproduces the patient's symptoms in association with marked bradycardia, hypotension, or both. The mechanism for this faint involves the Bezold-Jarisch reflex. Some patients may respond to treatment directed at blocking certain aspects of this reflex arc (for example, β-blockers to blunt the endogenous catecholamine release).

The prevalence of psychiatric disorders in patients with syncope may be much higher (as high as 24%) than previously thought. Psychiatric syncope appears to consist predominantly of panic disorders and major depression. These patients tend to be younger; report more prodromal symptoms such as lightheadedness, shortness of breath, dizziness, and palpitations; and experience syncopal symptoms almost weekly. The mechanism of psychiatric syncope is probably multifactorial and ranges from hyperventilation to vasovagal syncope. Diagnosing and treating the psychiatric disorder may alleviate syncopal symptoms in some patients.

In the 1980s, a considerable percentage of patients were left with a diagnosis of "syncope of unknown origin." In the 1990s, physicians have an array of new diagnostic tests to select from and use to decipher the exact cause and treat patients who present with syncope.

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Primary Human Immunodeficiency Virus Infection—Will You Miss the Diagnosis?

THE PREVALENCE of human immunodeficiency virus (HIV) infection continues to increase. Worldwide, 9 to 11 million people are infected with HIV; by the year 2000, 40 million people may be infected. A new, unpublished study by the San Francisco Department of Health found a higher prevalence of HIV antibodies among gay men in the 17- to 25-year-old group compared with older gay men. According to the Centers for Disease Control, the number of cases of the acquired immunodeficiency syndrome (AIDS) associated with heterosexual transmission of HIV has been increasing steadily. The number of AIDS cases in drug injectors, women, and children is also on the rise. Most seroconverters—53% to 93% of homosexual men with new HIV infection—will have symptoms of primary HIV infection, and most (87%) will seek medical attention. These facts indicate that physicians will continue to see patients who have symptoms of acute HIV infection.

Recent studies have shown that primary infection with HIV is associated with high plasma levels of virus, enhancing potential infectivity. In 1992, people at risk for infection will come from two categories of transmission: sexually transmitted and blood-borne. New cases of acute HIV infection will occur in heterosexuals and homosexuals with multiple sexual contacts and in sexual partners of persons at risk, especially intravenous drug users. Blood-borne infection remains a risk for fetuses, neonates, drug injectors, and, less so, for transfusion recipients and health care workers with needle-stick injuries. The early recognition of primary HIV infection is important to allow counseling to prevent transmission and to begin early treatment and monitoring that can increase the length and quality of life.

Primary HIV infection causes a mononucleosis-like syndrome, with or without aseptic meningitis, associated with seroconversion for the HIV antibody. The incubation period before clinical illness has ranged from five days to three months. Clinical manifestations are of sudden onset, may last 3 to 14 days, and include fever, pharyngitis, lymphadenopathy, arthralgia, myalgia, headache, retro-orbital pain, nausea, vomiting, diarrhea, anorexia, oral thrush or ulcerations, and an erythematous maculopapular rash. Neurologic manifestations include meningoencephalitis, myelopathy, peripheral neuropathy, and the Guillain-Barré syndrome. The syndrome can mimic influenza, rubella, infectious mononucleosis, toxoplasmosis, viral hepatitis, syphilis, herpes simplex infection, or aseptic meningoencephalitis. Laboratory evaluation at this stage is frequently not diagnostic. Abnormal liver function test results, especially elevated alkaline phosphatase and aspartate aminotransferase levels, have frequently been reported. The lymphocyte count declines initially, followed by an inversion of the CD4/CD8 ratio and a progressive decline of CD4 cells.

The antibody test for HIV using enzyme immunoassay can be negative, making early diagnosis difficult. One recent example is a 39-year-old heterosexual man who had been attending "sex orgies" with multiple partners, and six weeks later severe headaches, neck stiffness, hypersomnolence, myalgias, generalized weakness, malaise, anorexia, and weight loss developed. After a two-week illness, he sought medical attention. Examination revealed diffuse adenopathy and nuchal rigidity; the results of routine laboratory tests

were unrevealing. His initial HIV antibody test by enzyme-linked immunosorbent assay (ELISA) was negative.

A diagnosis of primary HIV infection depends on the detection of specific viral products or seroconversion. One method is an assay for the p24 antigen, a core protein of HIV-1. In the first few weeks after infection, there is an initial burst of virus replication with high serum levels of p24 antigen and plasma viremia. An HIV antibody response, however, may occur as early as 3 weeks or as late as 42 months after exposure to the virus. Screening for the HIV antibody is usually done using the ELISA test. In most laboratories, the more specific Western blot test will be done only to confirm a positive ELISA test but, in fact, the Western blot test may be positive days to weeks earlier. In patients with symptoms suggestive of acute HIV infection, it is important not to rely solely on the ELISA but to also request the Western blot and p24 antigen assay. In the case noted, when the patient was first seen, the initial Western blot result was indeterminate and the p24 antigen test was negative. The p24 antigen and Western blot tests were positive nine days later, but the ELISA test for HIV-1 antibody continued to be negative for four more days. Viral culture and the use of the polymerase chain reaction to detect HIV DNA sequences can also be diagnostic, but these tests are neither cost effective nor readily available. If an acute illness consistent with primary HIV infection remains undiagnosed, it is important to repeat the serologic tests to detect late seroconversion. Depending on the individual case, it would be reasonable to repeat the Western blot and p24 antigen assays weekly during the acute illness and monthly thereafter if the illness remains undiagnosed.

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Pressure Support Mechanical Ventilation

PRESSURE SUPPORT mechanical ventilation, first introduced ten years ago, is widely used and is now incorporated into most late-model ventilators, such as the Puritan-Bennett 7200 and the Siemens Servo 900C.

Pressure support assists spontaneous breaths initiated by patients on mechanical ventilators by maintaining a constant preset airway pressure throughout the breaths. Because the constant pressure is maintained only until inspiration stops, the patient determines both tidal volume and respiratory rate. Flow is initially high to reach the preset pressure rapidly, but it then slows continuously. In contrast, conventional assisted breathing maintains a constant inspiratory flow until a preset volume is reached; pressure increases continuously throughout the breath.

"Low-level" pressure support, with preset pressures of 4 to 8 cm of water, does the work necessary to overcome resistances of the endotracheal tube and ventilator circuit, decreasing the patient's work to approximate breathing without them. "High-level" pressure support, using preset pressures of more than 10 to 15 cm of water, decreases a patient's work further; pressures as high as 20 cm of water may be necessary to prevent fatigue.

Pressure support has many advantages over conventional assisted ventilation. It automatically limits peak airway pressures to a safe level. At any assist mode, pressure support decreases inspiratory muscle work and oxygen consumption by "pushing" gas into the lungs, decreasing a patient's need to "pull" gas in. The magnitude of this effect on work is dependent on the preset pressure level, which determines the ventilator flow rate and the ventilator's "push." Because a built-in microprocessor slows the flow rate progressively as alveolar pressure rises, there is better filling of poorly communicating portions of the lung. This improves ventilation-perfusion mismatch and oxygenation and increases lung distensibility and tidal volume. Because peak airway pressures are lower, cardiac output decreases less than with conventional assisted ventilation. For these reasons, and possibly because patients set their own breathing pattern, pressure support often provides greater patient comfort and thereby requires less sedation than either unassisted breaths or conventional assisted breaths. Finally, because the inspiratory muscles continue to do some work throughout inspiration, pressure support can provide graded muscle training during weaning trials.

Disadvantages include a need for more careful monitoring because minute ventilation may change if either lung resistance or compliance changes spontaneously; a lack of backup, unless used with intermittent mandatory ventilation; the failure of a breath to turn off if there is a leak in the system; and the need to provide additional pressure equal to the patient's positive end-expiratory pressure. Because the patient must trigger the ventilator, pressure support cannot be used to correct respiratory depression from drugs or to manage neuromuscular respiratory failure caused by muscle disease or disuse atrophy or fatigue.

It is desirable to assist spontaneous breathing with low-level pressure support when using intermittent mandatory ventilation or synchronized intermittent mandatory ventilation, because high inspiratory muscle work, oxygen consumption, and fatigue during spontaneous breaths may disastrously exceed even those during spontaneous breathing without a ventilator. Pressure support may also substitute for T-tube trials during weaning, possibly better simulating conditions following extubation.

Pressure support pressures not high enough to prevent fatigue are associated with palpable contraction of the sternocleidomastoid muscles; the pressure support should be increased until they are no longer palpable. Definitive information on whether pressure support is preferable to other methods for weaning is not yet available; anecdotal and physiologic evidence suggests that it is. Extubation is usually possible when a patient tolerates support of 4 to 8 cm of water, the pressure required to overcome equipment resistance.

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Cardiovascular Risk Factors in People Older Than 65

RISK FACTORS for the development of coronary heart disease and atherosclerosis have been well established for the middle-aged population. Only recently, however, has convincing evidence shown that all of the following are independent cardiovascular predictors in persons 65 years and older: total serum cholesterol, high- and low-density-lipoprotein cholesterol (HDL and LDL) and triglyceride levels, hypertension, left ventricular hypertrophy, glucose levels, physical inactivity, obesity, and cigarette smoking. These conclusions are derived from multivariate analyses of large, well-designed prospective studies, including the 30-year data from the Framingham Heart Study and the 12-year data from the Honolulu Heart Program.

The ratio of total and HDL cholesterol values and the HDL levels are much better predictors of coronary heart disease in elderly men and women than are LDL, total cholesterol, or triglyceride levels. The desirable ratio for men is less than 4.0 and for women is less than 3.5. Triglyceride is also a strong predictor in women and in some subsets of men. The combination of high triglyceride levels (greater than 150 to 200 mg per dl) and low HDL (less than 35 to 40 mg per dl) levels may represent a high-risk lipid profile even if the total cholesterol value is only 200 mg per dl. These findings suggest that, in patients older than 65, HDL is the most important lipid for predicting cardiovascular risk (more so than LDL) and that triglyceride levels are useful for further coronary heart disease risk stratification.

This information is an important "amendment" to both the 1987 National Cholesterol Education Program Expert Panel's and the 1983 National Institutes of Health Triglyceride Consensus Panel's lipid-lowering guidelines, which primarily emphasized coronary heart disease risk with LDL levels higher than 130 mg per dl and triglyceride levels higher than 250 mg per dl, respectively. Although no prospective studies to date have tested whether raising HDL levels is protective or whether HDL functions independently from LDL or triglyceride, studies have recently shown possible atherogenic mechanisms associated with hypertriglyceridemia, such as a positive correlation with small, dense, atherogenic LDL particles and a negative correlation with HDL levels. There is also an association between hyperinsulinemia and hypertriglyceridemia that may play a role in atherogenesis. Lipid-lowering dietary studies have shown significant reductions in CHD morbidity and mortality in the elderly, and clinical trials are under way to determine the efficacy of hypolipidemic drug therapies. Until such data become available, it is generally considered prudent, in addition to following the amended National Cholesterol Education Program guidelines, to recommend hygienic measures that raise HDL levels (and lower triglyceride levels), such as smoking cessation, weight reduction, and increased physical activity. Furthermore, the choice of all medications used in these patients should be evaluated for their favorable effect on HDL levels; secondary causes of hypertriglyceridemia (such as alcoholism, diabetes mellitus, and drugs) should always be excluded.

Isolated systolic hypertension (blood pressure 160 mm of mercury or higher), diastolic hypertension (blood pressure 90 mm of mercury or higher), and left ventricular hypertrophy are all independent risk factors for coronary heart disease in those older than 65. Left ventricular dysfunction, leading to congestive heart failure, is a leading cause of disability in this age group, which has a high prevalence of hypertension. Many well-designed controlled trials, such as the European Working Party on High Blood Pressure in the Elderly, have shown substantial reductions in cardiovascular mortality resulting from the treatment of combined systolic and diastolic hypertension. Most recently, the Systolic Hypertension in the Elderly Program study, which involved medically treating isolated systolic hypertension, has shown a significant reduction in total stroke incidence. Reductions in other major events were also noted.

Cigarette smoking—which is known to decrease HDL levels—increases the coronary heart disease risk in the elderly, especially if more than 40 cigarettes are smoked per day. Elevated blood glucose levels (greater than 130 mg per dl) are a major risk factor for the disease in men and women. Although the correlation is not as strong, both obesity (as defined by a relative weight of 130% or more by Metropolitan Life Insurance tables) and physical inactivity increase the risk of coronary heart disease.

Persons older than 65 constitute more than 12% of the United States' total population. They use 33% of all health care costs, most of which is directed toward the treatment of cardiovascular diseases. Encouraging international data have shown that significant reductions in coronary heart disease morbidity and mortality rates are occurring in older patients, even in those older than 74 years.

The Stockholm Ischaemic Heart Disease Secondary Prevention Study has even shown a reduction in overall mortality using lipid-lowering dietary and drug therapy. Advances in the understanding of cardiovascular risk factors and their contribution to an increased prevalence of coronary heart disease should encourage greater efforts toward modifying risk factors and possibly improving the quality of life in people older than 65.

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Benefits of Dual-Chamber Pacemakers

PACING THERAPY has progressed rapidly over the past 33 years from a major surgical procedure requiring a thoracotomy to one that can be safely and effectively performed at a community hospital under local anesthesia. There has been a concomitant increase in the understanding of cardiac physiology and the capabilities of implanted pacemakers. Pacemakers today are capable of pacing and sensing in both chambers of the heart to restore the normal coordination between the atria and ventricles while modulating the rate in

accord with physiologic requirements. These are called dual-chamber rate-modulated systems and are identified by the code DDDR. The increased complexity of these systems has led to difficulty interpreting electrocardiographic rhythms, an increased requirement for follow-up, and increased cost. Given these factors, it must be asked if these technologic advances are worth the additional costs. Because it is expected that a pacemaker will function properly for five to ten years, the long-term consequences of a pacing mode need to be considered when evaluating the cost.

Recent studies have shown that the maintenance of atrioventricular synchrony is associated with a dramatic reduction in the incidence of atrial fibrillation, systemic emboli, the development of overt congestive heart failure, and even mortality. In addition, adverse hemodynamic consequences of single-chamber (code VVI) pacing, originally thought to have an incidence of only 10% to 15%, are now being found in more than 80% of VVI-paced patients. The lower number reflects severe manifestations of the pacemaker syndrome that include overt congestive heart failure and syncope. The higher number identifies symptoms for which the body can compensate or with which the patient can learn to live but nevertheless affect the quality of life. These include palpitations caused by canon A waves resulting from the atrium contracting against a closed atrioventricular valve, increased mitral and tricuspid regurgitation, a nonproductive cough, symptoms of low cardiac output, and decreased cerebral perfusion resulting in an unsteady gait and periods of increased confusion. These symptoms may be intermittent.

The goal of treating a cardiac rhythm abnormality is to restore normal sinus rhythm. Sinus rhythm supports the heart rate at rest and accelerates with exercise while at all times maintaining synchrony between the atrium and ventricles. Dual-chamber rate-modulated pacing is the closest that technologic advances have come to mimicking normal sinus rhythm. Despite the increased costs associated with implanting the device, studies are documenting both the short- and long-term benefits of dual-chamber pacing. If the costs associated with repeated hospital admissions are considered—increased medication requirements and the quality of life associated with the late consequences of single-chamber pacing—dual-chamber pacing improves a patient's quality of life and becomes more cost effective. Several studies have shown that there is no longer justification to implant a single-chamber pacemaker in every patient who requires pacing therapy. The American College of Cardiology and American Heart Association guidelines state that

> long-term absence of atrioventricular synchrony increases the incidence of atrial fibrillation and stroke and may reduce patient life expectancy. . . . therefore, the concept that the single chamber pacemaker with adaptive-rate functions is equivalent to the dual chamber pacemaker cannot be supported.

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Diabetic Nephropathy Revisited

DIABETIC NEPHROPATHY is the leading cause of end-stage renal disease in patients with diabetes mellitus and is the single most frequent reason in the United States for starting long-term hemodialysis treatment. Diabetic nephropathy is defined by persistent proteinuria on a dipstick test (or greater than 0.3 grams per day urinary albumin excretion) in the absence of other renal disease. The prevalence of end-stage renal disease caused by diabetes ranges from less than 10% in patients with type II diabetes to about 40% in those with type I diabetes. Nonetheless, some groups with type II diabetes—such as African Americans, Asian Americans, Hispanic Americans, and Native Americans—have a much higher risk of end-stage renal disease than expected. Furthermore, diabetic patients with a family history of diabetic nephropathy or hypertension are at increased risk of nephropathy developing.

Therapeutic and preventive measures both aim at delaying the progression of diabetic nephropathy to end-stage renal disease. The control of hyperglycemia to "near normal" (tight control) is often considered an important first step in attempting to slow the progression of microalbuminuria to renal failure. Some renal mesangial changes regress with tight control and pancreatic transplantation. Although debate continues about the merits of tight control, poor glycemic control does strongly predict clinical diabetic nephropathy in diabetes. Once nephropathy is established, the control of blood glucose is ineffective in reversing the process.

Blood pressure control in patients with diabetes dramatically reduces the albumin excretion rate and slows the progression of renal failure. A loss of renal mass, as can occur in diabetic patients, results in compensatory glomerular hyperfiltration in the remaining nephrons. Although angiotensin-converting enzyme (ACE) inhibitors and some calcium channel blockers reduce the glomerular hyperfiltration, ACE inhibitors may worsen renal function and induce or worsen hyperkalemia in some patients.

Protein-restricted diets show promise in decreasing glomerular hyperfiltration and may play a role in therapy and prevention. Some studies show that such diets can decrease the urinary albumin content and delay the decline of creatinine clearance. Whether this results in the prevention of clinical renal failure over the long term remains controversial.

Other interventions proposed to slow the rate of progression of chronic renal failure in diabetic patients include platelet (thromboxane synthesis) inhibitors; phosphate-restricted, low-protein diets; vegetarian (no animal protein) diets; and aldose reductase inhibitors. The role of these interventions should be clarified in this decade.

In summary, diabetic nephropathy is a serious and costly problem. End-stage renal disease does not develop in all diabetic patients; why it does in some and not others is an enigma. Some preventive strategies are well established, and the aggressive control of even mild hypertension is essential. The increasingly diversified group of proteinuria-sparing drugs makes it easier to individualize care. It is prudent to maintain tight glycemic control, especially in patients with type I diabetes and in high-risk subpopulations of those with type II diabetes. A cautious use of any potentially nephrotoxic medication or intravenously administered contrast media is warranted. Protein restriction is highly advisable. Screening for proteinuria is recommended because it may

stimulate both physician and patient to be more diligent in their preventive regimen. Prevention is certainly better than cure, because no cure for established diabetic nephropathy is in sight.

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Treatment of Chronic Hepatitis C With Recombinant Interferon Alfa

NATURAL ALPHA INTERFERONS are host-derived proteins produced mainly by monocytes and B lymphocytes in response to viral and other stimuli. Because of its antiviral, antiproliferative, and immunomodulatory effects, interferon (IFN) has been used in the treatment of hairy cell leukemia, condylomata acuminata, and Kaposi's sarcoma associated with the acquired immunodeficiency syndrome. Advances in recombinant DNA technology have allowed the production of interferon alfa (IFN-α) in large quantities for clinical use. The Food and Drug Administration has recently added chronic non-A, non-B hepatitis (hepatitis C) to the list of approved indications for treatment with recombinant IFN-α2b.

Hepatitis C is responsible for more than 90% of cases of post-transfusional hepatitis and nearly half of the cases of sporadic hepatitis. About half of the cases of acute hepatitis C will lead to chronic hepatitis, and cirrhosis will develop in 20% of this group. In randomized, controlled clinical trials, 50% of patients with parenterally acquired chronic hepatitis C showed substantial improvement in serum alanine aminotransferase (ALT) levels when recombinant IFN-α2b was administered subcutaneously at a dose of 3 million international units three times a week for six months. This compared favorably with the 5% to 10% per year spontaneous remission rate in untreated patients. Of those responding to IFN-α2b treatment, 70% achieved reductions of ALT to normal levels. Relapse rates approached 50% within six months after the completion of therapy regardless of the dosage used. Retreatment with the initial dose regimen achieved a prompt remission in most patients. Transient elevations of serum ALT levels may occur in some patients after therapy is discontinued, but this by itself is not considered an indication for retreatment. Improvement determined histologically, primarily regression of lobular and periportal inflammation, was also observed in some patients. The presence of the neutralizing antibody to IFN, detected in the serum of some treated patients, did not have a demonstrable effect on the course of the disease or the response to therapy in the short term.

The most frequent side effects of IFN-α2b therapy are flulike symptoms (myalgia, headache, fever) that typically resolve after the first few doses. Other adverse reactions include diarrhea, alopecia, rash, altered mental state, depression, cytopenia, and deranged thyroid function. Reducing the dose temporarily usually ameliorates these symptoms. Current criteria for exclusion from IFN-α2b therapy include decompensated liver disease, cytopenia, other (nonviral) causes of liver disease, serious concurrent medical illness, pregnancy, the presence of antibodies to the human immunodeficiency virus, a previous organ transplant, renal failure, a history of neuropsychiatric problems, autoimmune disorders, and preexisting thyroid abnormalities if thyroid function cannot be maintained in the normal range by medication.

The effect of IFN-α2b therapy on viral replication, infectivity, and the long-term natural history of chronic hepatitis is not known. Current studies will show if higher doses or a longer duration of treatment with IFN-α2b will increase the frequency and duration of remission.

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Transesophageal Echocardiography

TRANSESOPHAGEAL ECHOCARDIOGRAPHY (TEE) has become an accepted clinical procedure and is considered a logical extension of a complete echocardiographic examination in selected patients. Access to the heart in almost all patients, safety, patient tolerance, and predictably high-quality images have fostered a wide application. Transesophageal echocardiography allows the evaluation of cardiac, valvular, and vascular structures and function in a relatively noninvasive manner. Imaging of the heart through the esophagus provides an unobstructed view of cardiac structures and the great vessels and allows the use of higher frequency transducers, which results in better image quality.

Transesophageal echocardiography examinations are done with an ultrasound transducer mounted at the tip of a modified gastroscope. It can be done in an echocardiography laboratory, in an emergency department, on regular wards, in intensive care units, and in an operating room. In conscious patients, the fasting time before the TEE study should be at least three to six hours. Endocarditis prophylaxis is applied to high-risk patients, especially those with prosthetic valves. Anticoagulation is no longer a contraindication. Patients are generally premedicated, especially those who are apprehensive. A regimen used in our laboratory is 1 to 2 mg of midazolam hydrochloride given intravenously. The posterior pharynx of each patient is anesthetized topically with a 14% benzocaine spray before the procedure.

Conventional transesophageal endoscopes allow imaging in the horizontal plane. Specific limitations of horizontal imaging include difficulty in visualizing extreme anterior and posterior structures and an inability to depict contiguous long-axis or off-axis spatial relationships. Because the heart is a complex organ with three-dimensional relationships and interrelated structures, the ideal tomographic imaging technology should delineate all three anatomic planes. Biplanar imaging has recently become available, adding an orthogonal longitudinal plane and thus enhancing the diagnostic poten-

tial of this technique. Biplanar imaging has now become the method of choice for completely delineating cardiovascular anatomy. The combination of these two planes is superior to either one plane in determining cardiac disease. Specific diagnostic areas of interest include native and prosthetic valves; tumors, thrombi, and vegetations; congenital cardiac defects; aortic aneurysm and dissection; and determining the source of embolism. Complete TEE evaluation of the aorta using a biplanar probe and pulsed Doppler and color flow imaging can diagnose the presence, extent, and type of aortic dissection in virtually every case, and results are comparable to those of computed tomographic scans and magnetic resonance imaging. The advantage of TEE over those techniques is that it can be done at the bedside and in a relatively short time. In addition, TEE can be used intraoperatively and has proved to be of considerable value in assessing the adequacy of a cardiac operation (such as mitral valve repair).

In most cases, TEE is best used as an adjunct to the standard transthoracic, two-dimensional, echo-Doppler examination. Although the clinical indications are rapidly evolving, this technique provides a higher diagnostic yield in patients with suspected endocarditis, prosthetic valve dysfunction, intracardiac thrombi and masses, and aortic dissection.

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Advance Medical Directives

FOLLOWING THE NATIONAL media attention to the Karen Ann Quinlan case, on January 1, 1977, California's Natural Death Act became the nation's first living will statute. More than 40 states have now enacted similar statutes. More than a decade later, despite widespread public endorsement, less than 10% of Americans have actually made a living will. Recent judiciary and congressional actions, however, should prompt physicians and patients to focus even more on implementing and documenting advance medical directives.

After the highly publicized Nancy Cruzan case, on June 25, 1990, the United States Supreme Court issued its first decision about the "right to die." The Court upheld that the state of Missouri could require "clear and convincing" evidence of Cruzan's wishes before allowing surrogates to authorize the termination of life-sustaining treatment. The continuation of tube feedings for a person in a persistent vegetative state was enforced, even though Nancy Cruzan's earlier statements suggested she would not want such feedings, her family believed she would not want them, and the Supreme Court acknowledged her parents' motives were loving and caring. Thus, the Supreme Court ruling rejected the traditional medical practice of allowing families to make decisions for incompetent patients.

In 1990, Congress passed the Patient Self-determination Act, which took effect on December 1, 1991. Under the law, hospitals, nursing homes, and health maintenance organizations that participate in the Medicaid and Medicare programs must, at the time of admission, provide patients with written information about state laws governing patients' rights to accept or refuse medical treatment and to formulate an advance medical directive. The written policies of the individual hospital or nursing home regarding the implementation of these rights and written documentation whether or not a patient has executed an advance medical directive must also be provided.

Faced with the implications of the Cruzan decision, physicians and patients must act now to avoid situations in which the law may impose restrictions on surrogate decision making. Advance directives, such as a living will, the natural death act, and a durable power of attorney for health care, allow patients to indicate treatments they might wish to have and to designate a surrogate in case they were to become incompetent. It is difficult for a living will to specify all possible treatments for a given circumstance, but a health care proxy allows for greater latitude in future decision making.

While the Patient Self-determination Act may force hospitals and physicians to address this issue with each patient on hospital admission, a better time to start considering this subject would be in the outpatient setting. There, without the distractions of an acute medical illness and allowing sufficient time for discussion and clarification between physicians and patients, along with any concerned family or friends, a more thoughtful decision could be reached for each person. Recent studies indicate that the vast majority of outpatients would welcome the opportunity. Few express anxiety about the topic, and most expect their physicians to initiate the discussion. To simplify the process, several proposals have been made to ease the process and to have forms readily understandable by the general public.

Physicians must begin to broach the topic of advance medical directives routinely and at the earliest possible date with each patient. Failure to consider a written advance medical directive may, in some states, result in unpleasant and prolonged court hearings or, worse, the imposition of life-sustaining treatment when it is no longer desired by the patient.

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Clinical Use of Erythropoietin

ERYTHROPOIETIN IS the glycoprotein hormone that regulates erythrocyte production. In the kidneys, specialized "oxygen sensors" detect the tissue delivery of oxygen and modulate the production of erythropoietin to maintain an erythrocyte mass that provides optimal oxygen transport for metabolic needs. Normal erythropoietin levels of 10 to 25 units per liter

are sufficient for replacing senescent erythrocytes in healthy persons. With severe anemia or hypoxia, erythropoietin levels may increase by three orders of magnitude in an effort to restore the red cell mass. An understanding of this feedback regulation is critical for the appropriate therapeutic use of erythropoietin and for the interpretation of new sensitive erythropoietin assays.

The physiologic responses to erythropoietin have been well studied, and, despite some early concerns, antibodies to erythropoietin have never developed in anyone. Erythrocyte production is stimulated as a function of both erythropoietin concentration and time: the intravenous administration of erythropoietin stimulates erythroid marrow less than the same dose administered subcutaneously, which results in lower peak levels but sustained concentrations. Although erythropoietin synthesis occurs within hours after renal hypoxia and it interacts quickly with its receptor on precursor cells, weeks are required for sufficient cellular proliferation to achieve a notable increase in the erythrocyte mass. Thus, erythropoietin therapy can be useful only in nonacute situations. A response to erythropoietin use should be measured as increased reticulocyte counts at seven to ten days, although responses can be seen as early as four days. The response to erythropoietin may be blunted by conditions that interfere with erythrocyte production, including deficiencies of iron, folate, or vitamin B_{12}; the presence of chronic inflammation; or with primary marrow disorders such as myelofibrosis, tumor infiltration, and myeloproliferative diseases.

Patients receiving erythropoietin should be monitored for problems as the hematocrit increases. A reversal of hypoxia-induced vasodilation may lead to hypertension and, if the changes occur too rapidly, to central nervous system disturbances, including seizures. Electrolyte abnormalities may occur as the cellular proliferation consumes potassium, calcium, folate, or iron.

The use of erythropoietin as replacement therapy is indicated for persons who cannot synthesize it, primarily patients with severe renal failure. Administering erythropoietin corrects their severe anemia and allows these patients to have sufficient oxygen-carrying capacity to enjoy normal activities. Maintenance dosing must be tailored for each patient, with the current recommendation of hematocrit concentrations in the mid-0.30s being based conservatively on relieving symptomatic anemia until clinical studies show how an improved hematocrit is related to the long-term complications of renal failure, such as peripheral vascular disease, atherosclerosis, and altered protein metabolism.

The concept of "relative deficiency" in erythropoietin production has proved clinically useful. For example, most patients with mild renal failure have anemia and circulating erythropoietin levels that are above "normal" but significantly lower than those of healthy persons who are phlebotomized to similar degrees of anemia. Replacement therapy to higher concentrations of erythropoietin further stimulates marrow production. Most patients with mild renal failure and symptomatic anemia will benefit from replacement therapy.

The concept of relative deficiency in marrow responsiveness to erythropoietin has led to other clinical uses. Patients with the acquired immunodeficiency syndrome in whom anemia develops during zidovudine treatment and patients with cancer, including those receiving chemotherapy, benefit from receiving erythropoietin. Whether substantial clinical benefit is achieved for these patients remains to be defined in randomized trials.

Autologous red cell transfusion for elective surgical procedures has become increasingly important. More units of erythrocytes can be collected from mildly anemic patients if erythrocyte production is stimulated with erythropoietin therapy. It is not yet clear whether erythropoietin therapy before an operation significantly reduces the need for postoperative transfusions or assists recovery from anemia.

Problems may arise when erythropoietin is used in persons with normal hematocrits. For example, its use by athletes to increase their oxygen-carrying capacity may have contributed to a number of unexplained deaths in long-distance bicycle racers over the past two years.

Understanding the full potential of erythropoietin therapy will come as appropriate patients are entered into properly designed clinical trials over the next few years.

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Alerts, Notices, and Case Reports

Cognitive Decline With Nortriptyline Use in a Patient With Dementia of the Alzheimer's Type

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ALONG WITH profound memory and cognitive impairment, patients with dementia of the Alzheimer's type frequently have personality changes, anxiety, depression, and agitation.[1] About 20% to 40% of patients with this dementia have symptoms of moderate to severe depression.[1-3] Depression may be more common early in the course of this condition.[4] Tricyclic antidepressants (TCAs) are frequently prescribed for patients with Alzheimer's-type dementia who have symptoms that suggest a depressive reaction. We report the case of a patient with probable dementia of the Alzheimer's type treated with nortriptyline hydrochloride for a depressive reaction. Nortriptyline therapy was associated with adverse effects resulting in impaired attention, concentration, short-term memory, attention to detail, and visual-spatial tracking.

Report of a Case

The patient, an active 71-year-old married, retired Air Force officer diagnosed with probable dementia of the Alzheimer's type four years earlier, sought admission to an investigational drug trial for this disorder. He was in good health with a previous history of resolved dermatitis and coronary artery bypass grafting in 1983. On initial presentation, he was taking nortriptyline hydrochloride, 75 mg, before bedtime, sublingual nitroglycerin, 0.4 mg (one tablet every other month), and one aspirin daily. He was taking no other prescription or nonprescription medications. Nortriptyline had been prescribed six months earlier for anxiety and sadness over the recent death of a sibling and his own cognitive losses. There were no changes in appetite, sleep, fatigue, restlessness, or suicidal ideation at the time nortriptyline was prescribed.

Admission criteria for the drug trial precluded the use of psychotropic medications. With his regular physician's consent, the nortriptyline dosage was tapered and the drug completely discontinued for a 30-day drug-free period. No serum nortriptyline concentrations were available. When the patient returned for further screening, his wife spontaneously described an increase in alertness, attention, and social involvement without nortriptyline, although he was more easily angered.

His medical records documented two previous administrations of neuropsychological testing. The Wechsler Adult Intelligence Scale-Revised (WAIS-R) and Trailmaking A and B were completed before the patient began nortriptyline therapy and again after six months of taking the drug. Because there had been precipitous cognitive decline on the second administration, the tests were repeated to determine whether cognitive function had declined, remained the same, or improved. The patient's score on a Mini-Mental State (MMS)[5] evaluation was 16 of 30 while receiving nortriptyline for six months. His MMS score improved slightly to 18 of 30 after the 30-day drug-free period. This was not clinically significant.

Figure 1 shows the results of the three administrations of the selected neuropsychological tests. Overall, the patient's performance declined after six months of taking nortriptyline and improved after it was discontinued. Digit Span, a subtest of the WAIS-R, is a measure of short-term auditory memory for number sequences and reflects attention span and ability to concentrate.[6,7] This patient showed above-average ability before nortriptyline use, below average while taking the drug, and a return to baseline after the drug was discontinued. Nonverbal reasoning, perceptual organization, and ability to process visual material are measured by the Performance IQ subscale.[7,8] Picture Completion, a subtest of the Performance IQ, measures alertness to visual detail and ability to grasp the meaning of visual details in a larger context.[5] Abstract problem solving and spatial relations are measured by the Block Design, and Digit Symbol task measures visual-

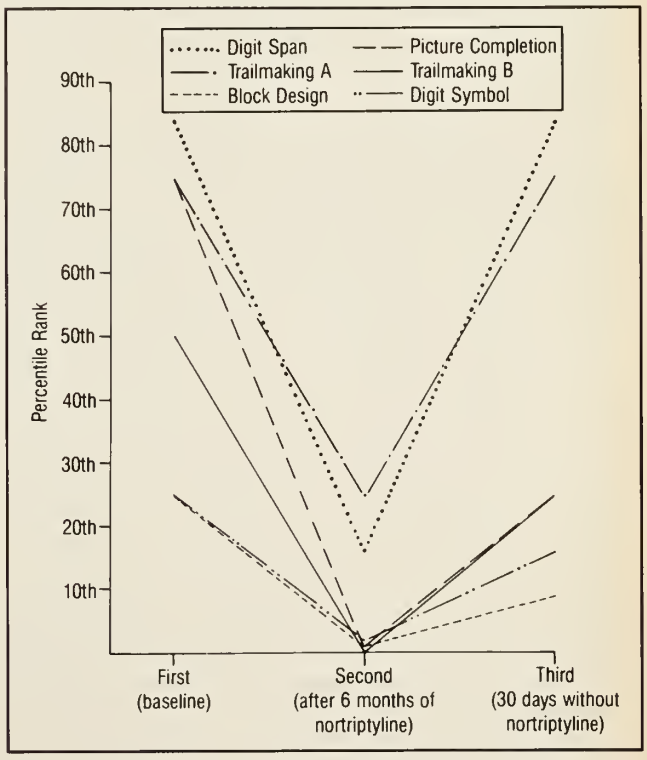

Figure 1.—The diagram shows the patient's performance on select neuropsychological tasks across the three evaluations before, during, and after nortriptyline hydrochloride therapy.

(Bartlomé P, King KS, Matsuo F, Wood JS: Cognitive decline with nortriptyline use in a patient with dementia of the Alzheimer's type. West J Med 1992 Jan; 156:75-77)

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ABBREVIATIONS USED IN TEXT

MMS = Mini-Mental State
TCA = tricyclic antidepressant
WAIS-R = Wechsler Adult Intelligence Scale-Revised

motor speed.[6,7] Ability on the Digit Symbol task is enhanced by short-term memory. The overall Performance IQ changed significantly across the three measurement points, suggesting that nonverbal ability declined while the patient was taking nortriptyline and improved subsequent to discontinuation. His performance on Block Design and Digit Symbol showed the same trend, although the change was of lesser magnitude.

Trailmaking A and B are measures of visual-spatial tracking under timed conditions and with increasing task complexity.[6] A decline in this task is a common finding among patients with dementia of the Alzheimer's type.[8] The patient's initial performance placed him in the 75th percentile on Trailmaking A and in the 50th percentile on Trailmaking B. While taking nortriptyline, his performance declined to the 10th to 25th percentile for Trailmaking A and he was unable to complete Trailmaking B. After nortriptyline use was terminated, his performance returned to baseline for Trailmaking A and to the 25th percentile for Trailmaking B.

Nortriptyline therapy in this patient resulted in measurable impairment in attention, concentration, short-term memory, attention to detail, and visual-spatial tracking. In addition, the MMS evaluation did not measure those cognitive functions that declined the most while this patient was taking nortriptyline. Although the neuropsychological tests are standardized, three different trained psychologists tested the patient under different conditions. Variations in testing scores could account for some of the differences seen. The direction of the results is consistent across the tests and subtests and congruent with the spouse's anecdotal reports.

Discussion

Tricyclic antidepressant agents may produce decrements in learning and memory in elderly patients.[9] A complex interaction may occur in patients with dementia of the Alzheimer's type and coexisting depression who receive these drugs. The anticholinergic activity of TCAs is responsible for cognitive impairment, which may either conceal improved cognition due to the alleviation of depression or result in further cognitive impairment due to neurochemical abnormalities associated with Alzheimer's-type dementia. Gross cognitive impairment is uncommon with TCA use at therapeutic serum concentrations.[10] Although subtle and specific disturbances of learning and memory can occur with lower dosages, these deficits may not be recognized. They contribute, however, to the patient's functional impairment unless cognition is evaluated.

Elderly patients are more susceptible than younger patients to the central nervous system anticholinergic effects of TCAs.[10-12] Further, elderly patients with dementia of the Alzheimer's type are more sensitive than age-matched controls to the effects of anticholinergic agents on tests of learning and memory.[13]

Cognitive impairment is related to TCA serum concentrations.[9,10] In general, elderly patients require a 50% reduction in the dosage of TCAs because of normal physiologic age-related changes that result in reduced metabolism and increased sensitivity to the drugs.[4,10,11] In this case the patient was maintained on a regimen of 75 mg of nortriptyline daily, a dose more appropriate for a young, healthy adult. Because there were no nortriptyline serum concentrations available, nortriptyline toxicity cannot be ruled out. The dramatic decrease in his cognitive performance may not have occurred on a lower, more appropriate dose.

Few studies have used specific neuropsychological tests to document cognitive impairment in patients treated with TCAs. Most studies commonly rely on the Mini-Mental State evaluation, which may not be specific or sensitive enough to detect cognitive changes, as evidenced by this patient. In a double-blind study using imipramine hydrochloride for depression in patients with Alzheimer's-type dementia, the MMS scores of all subjects improved although activities of daily living and other cognitive measures declined.[14] In another report, administering 50 mg of amitriptyline hydrochloride resulted in impairment on cognitive skills performance tasks such as the vigilance task, the divided attention task, and the critical tracking task.[15] In another study, the use of amitriptyline produced sedation and impaired coordination and cognitive performance such as digit substitution.[16]

Additional studies using specific neuropsychological testing are required. The ability to determine cognitive decline in patients with dementia of the Alzheimer's type would be useful in assessing possible benefits versus risks in prescribing psychotropic drugs. Until adequate controlled studies have been completed, some guidelines can be offered. First, patients presenting with symptoms of both depression and dementia require a thorough workup including neuropsychological testing. A limited cognitive assessment using the Dementia Rating Scale[8] establishes a baseline useful in evaluating change over time and response to treatment. Second, not all patients with Alzheimer's-type dementia who have depressive symptoms meet the criteria for a major affective disorder.[1] This patient was probably experiencing a grief reaction. Similar patients may benefit from psychotherapy rather than medication.[17] Selected patients with Alzheimer's-type dementia become more grief stricken than biologically depressed and may benefit from an opportunity to talk about their losses. Our experience and that of others[1,17] indicate that these patients are able to establish relationships with professionals. Third, some patients with Alzheimer's-type dementia do experience depression requiring pharmacologic treatment. Elderly patients generally require a 50% reduction in TCA dosage compared with young adults[10,11] because of changes in clearance, volume of distribution, and the elimination half-life. Elderly patients do achieve normal therapeutic serum concentrations with lower dosages. Patients with Alzheimer's-type dementia may require even lower dosages of the TCAs.[12] Serum concentrations for nortriptyline and imipramine are reliable and useful in evaluating efficacy and response and avoiding unnecessary cognitive impairment or toxicity.

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The Physician as Erotomanic Object

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EROTOMANIA, or De Clérambault's syndrome, attracts attention from several perspectives: nosological, psychological, and biological.[1-3] De Clérambault's syndrome borrows its name from the 20th-century French psychiatrist who described "psychose passionelle"—a condition whose central feature is a delusion in which usually a woman believes that an older man of higher social status is in love with her.[1,4] The traditional definition of De Clérambault's syndrome as being a predominantly female condition has not been borne out, however.[5,6] The most recent psychiatric nosology, *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R), has carved out a specific niche for De Clérambault's syndrome as a delusional (paranoid) disorder, erotomanic type.[1,7]

Perhaps the most vexing dilemma raised by this condition is the forensic one. Erotomanic persons cause significant problems for the misinterpreted object of their delusion. A perusal through newspapers and popular magazines finds many articles reporting the escapades or criminal acts of persons whose erotomanic targets are celebrities and politicians. From a forensic perspective, the two most recently prominent persons possibly suffering from erotomanic delusions have been John Hinckley, Jr, who attempted to assassinate then-President Reagan, and Prosenjit Poddar of the landmark legal case of *Tarasoff v. Regents of University of California*.[6]

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Physicians have not been exempt from becoming the object or target of an erotomanic delusion.[8-10] We describe the case of a male patient in whom an erotomanic delusion developed involving his female physician. We then explore the possible psychiatric-legal interventions and unresolved issues in these cases.

Report of a Case

The patient, a 39-year-old, never married, Syrian-American man, was involuntarily admitted to hospital for presenting a danger to his 40-year-old married, Syrian-American family physician, his erotomanic object. The patient first encountered the physician seven years ago after he took his mother to the physician's office for monthly visits after a stroke. The physician later became his personal physician as well. About a year before his psychiatric hospital commitment, the delusion developed that there was a romantic relationship between the physician and the patient as a result of his belief that she was secretly falling in love with him. Over the next several months, he made many telephone calls to the physician, sent her a "love letter" by registered mail, and sent her numerous gifts, including an engagement ring. He spent a great deal of time at the hospital where the physician attended patients and at her hair salon. Because the patient did not comply with the physician's requests to leave her alone, she obtained a restraining order to allow for his arrest if he continued to contact her. The patient remained undeterred and made several attempts over the next several months to contact her to complain about the restraining order. He not only telephoned and paged her answering service but continued to visit her office and the hospital. Four months after the restraining order was filed, on Valentine's Day, the patient sent the physician a Valentine's Day card with a letter accusing her of "gross misconduct," "mismanaging his mother's care," and having "played" on his emotions. He signed the letter, "love always." He was arrested about a month later for violating the restraining order. While in jail, he telephoned the physician and demanded to see her alone "to avoid the inevitable."

This patient had no previous psychiatric contact before the onset of his erotomanic delusion. About a year before the development of his delusion, he began to file lawsuits against various insurance and aerospace companies and believed that he was being monitored by overhead helicopters, that his phone was tapped, and that his apartment had been burglarized with his legal papers being the only items stolen. He had traveled to Washington, DC, to report this harassment to government authorities. He was not given an audience, however, because he had failed to make an appointment. The patient had no history of substance abuse or major medical problems. Although he had completed 2½ years of college, for the past few years he had been able to work only part-time in unskilled jobs and had lived with his elderly mother. He denied having auditory hallucinations.

After his arrest, it was decided that involuntary hospitalization on the basis of posing a "demonstrated" danger to others (California Welfare and Institutions Code §§5300 et seq) for a period of 180 days would be preferable to any legal sanction that could be obtained for a first-offense violation of a restraining order. In addition, treatment of the patient's psychosis could be attempted with hospital admission. The petition for this 180-day involuntary commitment was sustained during a jury trial.

Discussion

This patient suffered from a psychotic disorder manifested by a prominent erotomanic delusion. The DSM-III-R diagnostic possibilities are schizophrenia, paranoid type, and delusional disorder, erotomanic type, with the former being more likely. Notwithstanding any diagnostic ambiguity, the important forensic feature and clinical symptom of his psychotic disorder were his erotomanic delusion and the maladaptive and disturbing behavior arising from it.

Patients in whom an erotomanic attachment to their physicians develops have had actual contact with their erotomanic object. This contrasts to the type of erotomania that develops from afar with celebrities and political figures. The development of an erotomanic delusion involving a person's psychiatrist or other nonmedical psychotherapist can be explained in part as the result of the activation of a transferential relationship that develops within the context of psychological treatment. While nonpsychiatric physicians do not usually develop strong transferential relationships with their patients, they are seen by patients as intelligent, successful, omnipotent, and caring. Because erotomanic patients have generally been unattractive and unsuccessful persons,[1] the selection of a physician as a target can be understood as a psychotic attempt to compensate for the patient's low self-esteem.

Erotomania itself does not generally become a concern for the erotomanic object until the delusional person begins to act on his or her delusion. Before this occurs, any disturbing behavior by the delusional person is generally unknown to the target. The situation becomes difficult when the delusional person perceives rejection from the erotomanic object and decides to vent anger. Even when confronted with the fact that the erotomanic target is not in love with him or her, the delusional person can reason that the erotomanic object behaves paradoxically to disguise true love.[2] The case reported here illustrates the futility of trying to discourage delusionally driven actions, even though the physician was married and had obtained a restraining order against the patient. Less than 5% of erotomanic persons probably do physical harm (Park Elliot Dietz, MD, MPH, PhD, Clinical Professor of Psychiatry, UCLA School of Medicine, oral presentation at a meeting of the Southern California Chapter of the American Academy of Psychiatry and the Law, June 2, 1990). Nonetheless, the inability of the delusional person to cease the maladaptive behavior coupled with the development of a perception of rejection sets the stage for possible physical violence.

If a physician discovers that he or she is the erotomanic target of a patient, an attempt at psychiatric intervention is indicated. If the patient has a psychiatrist (or psychotherapist), the care giver should be contacted. Otherwise, an attempt should be made to refer the patient for psychiatric evaluation. Even if the patient is actively involved in psychiatric treatment, results have not been particularly encouraging.[4] For patients with schizophrenia or a delusional disorder, the only effective treatment has been neuroleptic medication. Even this has not always been successful in diminishing or eliminating erotomanic delusions.[1] If the patient is not involved in psychiatric treatment and continues to present as a behavioral problem, more drastic measures must be implemented. The first is to obtain a restraining order to allow legal action if the erotomanic patient continues to interfere with the physician's professional or personal life. Although there is some risk that a restraining order may exacerbate the erotomanic behavior,[11] this may happen without any intervention by the target. If the delusional patient disregards the restraining order, intermediate-term involuntary commitment can be attempted, as in the case of this patient. Because treatment may not be successful, involuntary commitment may be the only effective method to separate the delusional person from the target.[6]

Obtaining immediate-term involuntary commitment is the best our society can do in dealing with erotomanic behavior. Long-term or indefinite commitment is possible only if a person continues to pose a statutorily defined level of danger. Because many persons in such an adversarial setting could hide their erotomanic beliefs[11] and act in accordance with hospital rules, long-term commitment is not likely to occur. The hope is that the delusional person will be sufficiently discouraged by immediate-term involuntary commitment to discontinue any further involvement with the erotomanic target. Unfortunately, our present system cannot always prevent a tragedy from occurring. Wholesale preventive detention of erotomanic persons is not legally or ethically justifiable, unless all, including physicians, are willing to forego constitutional guarantees. While physicians can take measures to protect themselves, such as home and office security measures, security-conscious travel, restricting access to the home address, and the use of self-defense weapons,[12] these precautions may appear overly draconian.

While physicians infrequently become erotomanic objects of their patients, the problem should not be underappreciated. It is an important warning signal for definitive action. Physicians also need to be aware of the related nondelusional erotomania or obsessive love that can be as troublesome as the delusional erotomania shown by the case reported here.[11,13,14] While treatment of the underlying mental disorder may not always be successful, early recognition and psychiatric and legal interventions may forestall tragedy. This case illustrates the infrequent but highly troublesome conundrum faced by the physician who is a patient's erotomanic object.

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Occult *Enterobacter aerogenes* Pneumonia Diagnosed by Indium 111-Labeled Leukocyte Scan

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OCCULT INFECTION is a common clinical challenge in intensive care units but is uncommonly ascribed to pneumonia, which is usually excluded by a normal chest roentgenogram. Exceptions include *Pneumocystis carinii* pneumonia and tuberculosis,[1,2] as well as bacterial pneumonia in neutropenic patients, all of which may present with initially clear lung parenchyma on a chest radiograph. Among the imaging techniques that have been proposed to identify the site of occult infection are computed tomography (CT), magnetic resonance imaging, and radiolabeled isotope scans using both gallium 67 and indium 111-labeled leukocytes, the latter of which has been found to be variably effective for diagnosing lung infection, such as pneumonia and abscess.

To extend the recognized spectrum of occult pulmonary infections that may be truly occult and to emphasize the value of [^{111}In]leukocyte scans in their detection, the following report demonstrates the use of [^{111}In]leukocyte scanning to localize an occult pneumonia due to *Enterobacter aerogenes* in a ventilator-dependent, non–immunocompromised patient.

Report of a Case

The patient, a 68-year-old man, was admitted to an outlying hospital with acute, severe low back pain. A CT scan of the abdomen revealed a leaking abdominal aneurysm, and the aneurysm was repaired using aortobifemoral graft placement. His postoperative course was complicated by cardiac arrest with cardiogenic pulmonary edema leading to respiratory failure, renal failure, and fever of an unknown origin. His medical history included atherosclerotic heart disease, peripheral vascular disease, type II diabetes mellitus, heavy smoking with presumed chronic obstructive pulmonary disease, and a history of histoplasmoma diagnosed by wedge resection.

On transfer to the Cleveland Clinic Hospital ten days after the operation, the patient was obtunded and required mechanical ventilation. Laboratory evaluation showed a leukocytosis—15.3×10^9 per liter (15,300 per μl)—and tracheobronchial secretions showed few neutrophils but a moderate growth of *E aerogenes*. The parenchyma on the chest roentgenogram was clear. Therapy with vancomycin hydrochloride and ceftazidime had been begun for fever and leukocytosis at the referring hospital but was discontinued on arrival, with cultures of blood and urine done after antibiotics were discontinued failing to grow organisms. Another CT scan of the abdomen showed no suggestion of graft infection, and the sections through the lower chest were normal. In an effort to identify a presumed occult infection, a scan using ^{111}In autologous/oxine-labeled leukocytes was done (Figure 1). It showed grade III (intensity of uptake equal to liver) uptake in the lungs at a time when the lung parenchyma on chest x-ray film from the same day was interpreted as normal (Figure 2). The [^{111}In]leukocyte scan was taken 24 hours after administering autologous leukocytes labeled with a dose of 500 μCi of ^{111}In. The labeled cells were administered within two hours of procurement, and scanning was completed by a Siemens Bodyscan dual-head imager.

To pursue further the possibility of occult pulmonary infection, a bronchoscopy was done the following day with right lower lobe bronchoalveolar lavage. Analysis of the lavage fluid revealed 525 per μl of erythrocytes and 153 per μl of leukocytes. The differential cell count was polymorphonuclear leukocytes, 0.23; lymphocytes, 0.03; monocytes, 0.04; and alveolar macrophages, 0.69. Cultures of the lavage fluid grew 10^4 colony-forming units (CFU) per milliliter *E aerogenes* and 10^5 CFU per ml γ-*Streptococcus* species. Sensitivity analysis showed the *E aerogenes* organisms to be resistant to semisynthetic penicillins and cephalosporins but sensitive to both ciprofloxacin and the combination of trimethoprim and sulfamethoxazole. The combination drug was administered at a dose of 200 mg intravenously every eight hours (dose reduced because of renal insufficiency). Sensitivities of the *Streptococcus* species were not tested because the organism was interpreted as normal mouth flora. After three days, the patient defervesced and was weaned from mechanical ventilation over the next week as his mental

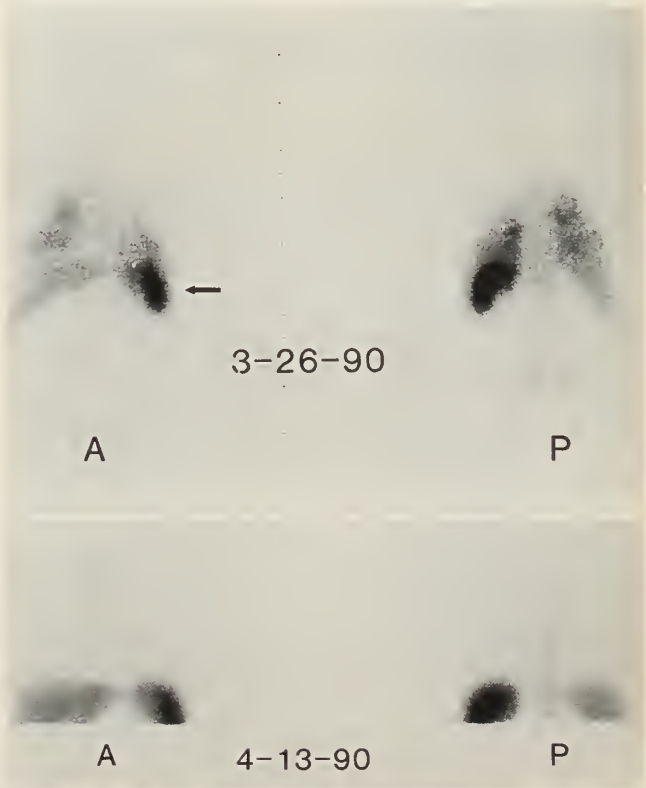

Figure 1.—Top, An indium 111-labeled leukocyte scan (24 hours) on hospital day 9 shows grade III uptake in both lung bases and in the right mid-lung zone. Splenic uptake **(arrow)** is grade IV. **Bottom,** A follow-up [^{111}In]leukocyte scan on day 27 shows clearing with treatment.

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ABBREVIATIONS USED IN TEXT

CFU = colony-forming units
CT = computed tomography

state improved. Chest radiographs during this time continued to show clear lung parenchyma (Figure 2), and a repeat [^{111}In]leukocyte scan 16 days after treatment showed no evidence of pneumonia (Figure 1). He was discharged to home 73 days after admission to the hospital.

Discussion

[^{111}In]Leukocyte scans are most widely used in evaluating occult infections, especially when intra-abdominal abscess or osteomyelitis is suspected.[3] As reviewed in Table 1, the uptake of radioactive indium has also been reported in a wide range of pulmonary problems.[4-17]

Figure 2.—Top, A posteroanterior chest radiograph on hospital day 9 shows clear lung parenchyma despite concurrent lung uptake of radioactive indium (Figure 1). **Bottom,** A follow-up posteroanterior chest radiograph was taken on day 25.

In assessing the uptake of ^{111}In, which is normally taken up by liver, spleen, and bone marrow, the degree of uptake is graded on a scale from I to IV.[4] Grade I reflects uptake greater than that of soft tissue but less than that of rib, grade II reflects uptake equal to that of rib but less than that of liver, grade III reflects uptake equal to that of liver, and grade IV reflects uptake equal to that of the spleen.

The time course of leukocyte recruitment after the onset of lung infection is also relevant and helps explain the diagnostic performance of [^{111}In]leukocyte scans in evaluating chest infections. After inducing pneumococcal pneumonia in dogs, Dutcher and co-workers have shown that leukocyte recruitment to the lung begins within hours of exposure to pneumococci and is complete within 24 hours.[18] Autoradiographs of resected lung within 24 hours of aspiration reveal labeled leukocytes filling consolidated alveoli, but more delayed administration of ^{111}In will not produce chest uptake, presumably because leukocyte recruitment is complete by that time.[9]

[^{111}In]Leukocyte scanning has proved appealing in diagnosing extrathoracic occult infections because the reported diagnostic sensitivity ranges from 73% to 88% and the specificity ranges from 90% to 97%.[4,18,19] The current report highlights the sensitivity of [^{111}In]leukocyte scans in diagnosing chest infection, as the radioisotope uptake was the only indicator of a true pneumonia in our patient. Three lines of evidence support this conclusion:

- Retrieval of a substantial bacterial growth ($\geq 10^4$ CFU per ml) from bronchoalveolar lavage fluid;
- Defervescence in response to antibiotic therapy (trimethoprim-sulfamethoxazole) tailored to the bronchoalveolar lavage culture results (notably *E aerogenes*); and
- Disappearance of the chest uptake of [^{111}In]leukocytes when the radioisotope scan was repeated after the patient's defervescence.

Reported experience with [^{111}In]leukocyte scans in diagnosing chest infections has been mixed, with some investigators emphasizing poor specificity (false-positive lung uptake),[5,8] and others reporting disappointing sensitivity (false-negative ^{111}In scans in patients with true chest infections).[9] For example, in a recent review of 345 patients who underwent [^{111}In]leukocyte scans, 12% of patients had low-grade chest uptake without evidence of concomitant chest infection (low specificity).[3] As with any diagnostic test, the diagnostic performance (sensitivity, specificity, and predictive values) varies with the criteria for a positive test. A review of available experience with indium scanning in chest infections (Table 2) suggests that the more focal the ^{111}In uptake in the chest, the greater the predictive value of an abnormal ("positive") scan for a true chest infection. Though less well studied, the diagnostic accuracy of ^{111}In scanning also improves as the intensity of uptake in the chest increases—for example, to grades III and IV uptake.

Other investigators have reported normal ("negative") [^{111}In]leukocyte scans in patients with known chest infections, including those with empyema, miliary tuberculosis, and pneumonia. In a series reported by Saverymuttu and colleagues, five patients with lobar pneumonia lacked chest uptake of ^{111}In despite evidence of preserved pulmonary perfusion and extrathoracic uptake of the isotope.[9] The putative

TABLE 1.—*Pulmonary Conditions in Which Indium 111-Labeled Leukocyte Uptake Has Been Reported*

Type of Pulmonary Disorder	*Source*
Infectious	
Pneumonia	McAfee and Samin, 1985[4]; Segall and McDougall, 1986[5]; Ascher et al, 1979[6]; Alderson et al, 1983[7]
Lung abscess	McAfee and Samin, 1985[4]; Cook et al, 1984[8]; Saverymuttu et al, 1985[9]; Massie and Winer-Muram, 1986[10]
Cystic fibrosis	Crass et al, 1979[11]
Bronchiectasis	Currie et al, 1987[12]
Empyema	McAfee and Samin, 1985[4]; Segall and McDougall, 1986[5]; Cook et al, 1984[8]
Septic emboli	McAfee and Samin, 1985[4]
Infected central venous line	McAfee and Samin, 1985[4]
Inflammatory, noninfectious	
Adult respiratory distress syndrome	Cook et al, 1984[8]; Segall et al, 1987[13]
Oxygen toxicity	Alderson et al, 1983[7]; Rinaldo et al, 1988[14]
Pulmonary embolism	Segall and McDougall, 1986[5]
Aspiration	Cook et al, 1984[8]
Inactive cytomegalovirus infection	Forstrom et al, 1981[15]
Postradiation therapy	McAfee and Samin, 1985[4]
Wegener's granulomatosis	McAfee and Samin, 1985[4]
Noninflammatory	
Congestive heart failure	McAfee and Samin, 1985[4]; Cook et al, 1984[8]
Atelectasis	Cook et al, 1984[8]
Cell clumping from dose agitation or from injection into glucose solution	Coleman and Welch, 1980[16]; Simerman et al, 1986[17]
Tumor or metastasis	Segall and McDougall, 1986[5]; Cook et al, 1984[8]
Sterile pleural effusion	Segall and McDougall, 1986[5]
Pulmonary hemorrhage	Segall and McDougall, 1986[5]
Increased interstitial markings	Segall and McDougall, 1986[5]
No associated thoracic disease	McAfee and Samin, 1985[4]; Segall and McDougall, 1986[5]; Cook et al, 1984[8]

reason for the "false-negative scans" in this series is that granulocyte recruitment to the lung that is necessary for a positive scan was already completed by the time the scan was done, hence, a falsely negative radioisotope study. Specifically, all five patients had chest symptoms of pneumonia for at least two days before the [^{111}In]leukocytes were administered, considerably longer than the 24-hour period in which granulocytes migrated to the chest after initial infection in dogs.[5] In contrast to the low sensitivity in already established pneumonia, [^{111}In]leukocyte scans have proved sensitive in patients with bronchiectasis. Specifically, in one series, 18 patients with severe bronchiectasis and persistent sputum production were studied, of whom 16 had increased uptake of [^{111}In]leukocytes within 24 hours of injection.[12] Radioisotope uptake gravitated to regions of moderately severe bronchiectasis on CT scans, and ^{111}In radioactivity correlated roughly with the volume of 24-hour sputum production. Unlike the rapid consolidative process in lobar pneumonia, bronchiectasis is characterized by repeated cycles of infection and resultant inflammation in which granulocyte recruitment to the lung is ongoing.

As with the case reported here, several earlier reports have shown true-positive [^{111}In]leukocyte scans in patients with clear chest radiographs. In a retrospective analysis of 128 patients undergoing [^{111}In]leukocyte scanning for suspected abdominal abscesses, 58 patients had positive scans, of whom 20 (34%) had unexpected extra-abdominal sites of uptake. Of these 20 patients, 3 had pneumonitis initially diagnosed by ^{111}In uptake, though the precise confirmatory method of diagnosing pneumonia in this series is unspecified. In another report, grade IV focal uptake of ^{111}In was reported with aspergillar pneumonia in a heart transplant patient whose pneumonia was evident only as a nodular infiltrate on chest CT scan. Autopsy-proved cytomegaloviral pneumonia was reported in a renal transplant patient in whom infiltrates developed on a chest radiograph two weeks after ^{111}In uptake in the chest was first evident.[12] The use of [^{111}In]leukocytes in the diagnosis of cytomegalovirus pneumonia was also recently reported in a renal transplant recipient with a normal chest roentgenogram.[21]

The current report extends this available experience and provides another challenge to the notion that the chest uptake of radioactive indium in a patient with a clear chest radiograph presents a false-positive scan. More systematic prospective study will be necessary before the diagnostic accuracy of [^{111}In]leukocyte scans for chest infection can

TABLE 2.—*Diagnostic Accuracy of [^{111}In]Leukocyte Scans for Chest Infections in Available Series**

Study	*No. Scans Positive/ Total No.*	*Sensitivity, %*	*Specificity, %*	*Positive Predictive Value, %*	*Negative Predictive Value, %*
Cook et al, 1984[8]	48/48	NA	NA	33	NA
	27/48†	NA	NA	52	NA
McAfee and Samin, 1985[4]	22/22	NA	NA	64	NA
	13/22†	NA	NA	100	NA
Seabold et al, 1984[20]	3/128	74	100	100	99
Segall and McDougall, 1986[5]	68/155‡	92	66	35	98
	11/155§	38	99	91	89
	23/155†	35	89	39	87

NA = not available

*Only positive scans were examined. †Focal uptake. ‡All grades. §Grade III or IV.

be ascertained, but our experience suggests that the chest uptake of this radioisotope in the context of occult infection warrants further diagnostic surveillance for the possibility of pneumonia.

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Commentary

Communicating Bad News

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Communicating bad news in the clinical setting is difficult. Sometimes the patient, family members, and the physician telling the bad news feel upset and resentful for long periods thereafter. Yet research has emphasized the need for patients to be told bad news, or at least to be offered the opportunity to hear it.[1,2] Medical schools are attempting to incorporate teaching this communication into their curricula,[3,4] and specialty groups such as anesthesiologists,[5] oncologists,[6,7] and others[8-21] are beginning to address the issue as well. Despite the importance of this function, which falls to almost all clinicians, no clear research is available to guide this process, and little has been written to help practitioners deliver bad news in the most constructive manner possible. This article offers suggestions that we have found useful in helping physicians deliver bad news.

The physician's goal, not always attainable, is to fully inform the patient and family so that they are able to comprehend the clinical situation and make sound decisions consistent with their beliefs and ideals. Physicians can experience a great deal of personal satisfaction when the patient and family can be helped through a difficult time.

Bad news can involve a variety of things: a positive test for the human immunodeficiency virus, a heart attack, death of a family member, a recommendation for a surgical procedure, loss of a pregnancy, the need for a prolonged hospital stay. Anything that changes a person's view of the future in a negative way is bad news. For example, one of our most distraught and inconsolable patients had been given the diagnosis of herpes. The physician should remember that bad news, like beauty, may be "in the eye of the beholder."

Communicating Bad News to Patients

The setting and timing of the communication are important aspects of telling bad news. Unfortunately, the health care system often works against the physician in this regard. Specifically, physicians are often called on to deliver bad news to patients they have not previously met or do not know well, such as in an emergency department or a teaching hospital where house officer rotations may cause a trusted resident to leave the patient at a crucial time. Physicians often feel too busy to spend adequate time with a patient. Time spent counseling patients is not reimbursed at the same rates as time spent doing procedures. Although the system may work against it, we urge physicians to consider both the setting and timing when telling bad news.

The setting helps establish the tone of the interaction. We urge physicians to find a quiet place away from others to talk with patients. For example, leave a pager with a colleague for 10 to 15 minutes so that the talk will be undisturbed. Sit down and talk directly to the other person. What will be said is often among the most important communications the patient or family has ever heard, and they can feel slighted and uncared for if the physician is allowed to be distracted during this time. People find it comforting to receive their physicians' full attention and concern.

We strongly recommend that bad news not be given over the telephone. A recent study of patients hearing the news of cancer found that 23% were told over the phone.[22] Significantly, 76% of patients told in the office or hospital room rated their physicians as "helpful" in aiding them to understand their illness, while only 48% of those told on the telephone or in the recovery room rated their physicians in this way. For example, one patient told by phone reported that

> [The doctor telephoned to say] . . . "the bad news is you have a tumor. The good news is we think it's a meningioma which means it's easy to get to." But, meanwhile, I'm standing there with the phone and my mouth down to the floor saying, . . . "What do you mean?" and asking him if I could come in to meet with him. And he said, well he could see me next Tuesday. This was Thursday . . . . It still amazes me that a person could do that.[22(p586)]

In sum, we urge physicians to sit down with the patient and family members in a quiet setting, giving their full attention to conveying difficult and often painful information.

The timing of breaking bad news is also extremely important. If at all possible, a time should be chosen when the physician is feeling rested and emotionally able to deal with the situation. Avoid situations wherein the physician has been up all night or must rush off to finish rounds or to an appointment, meeting, or conference. Similarly, a time should be chosen when the patient is able to hear the news. For example, bad news should not be delivered immediately following a difficult medical procedure, when a patient's thinking may be clouded by medication, or when he or she is in pain or otherwise symptomatic, severely anxious, or depressed. If family members, counselors, or members of the clergy are involved with the case, a time should be chosen when they are available to support the patient after he or she hears the news. When possible, patients should choose who should be present when the information is divulged. Our recommendation is that the breaking of bad news should be timed to maximize the strength of all persons involved.

If there is a language barrier between the physician and the patient, a hospital or clinic interpreter should be used to translate, rather than a family member. We advise that physicians talk to the interpreter before the interview, making sure the interpreter understands the clinical situation and the physicians' goals for the discussion. The person doing the translating may have limited medical training, and precise communication may get lost in the emotions of the moment.

(Miranda J, Brody RV: Communicating bad news. West J Med 1992 Jan; 156:83-85)

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Also, translators have feelings, too, to which the physician must be sensitive.

Choosing what to say to a patient is perhaps the most important aspect of communicating bad news. First, the patient should be asked how he or she is feeling; the physician should not try to break bad news at a bad time for the patient. We suggest that the physician warn the patient that he or she has something serious to talk about. Often it is appropriate to say to the patient that this is going to be difficult for both. Then stop, monitor the effects of these words, and assess the patient's receptivity to the communication. We then suggest that the physician tell the patient the news in the most straightforward but compassionate way possible, using simple language, avoiding terms that the patient is unlikely to understand. The news should be told directly. Start with less emotionally charged words, but use the real words—cancer, AIDS, heart attack—at some point. Patients have been known to report later, "They told me I had a growth [or tumor or malignancy or adenocarcinoma], but nobody ever told me I had *cancer*." For example, a dialogue with a patient may proceed as follows:

PHYSICIAN: *Good morning, Mr Lee. How are you feeling today?*
PATIENT: Better than I did a week ago.
PHYSICIAN: *I'm glad of that. We have some very serious matters to discuss regarding your health. Do you feel ready for this discussion?*
PATIENT: Well, I want to know. I'll try to be ready.
PHYSICIAN: *It's hard to ever be ready for difficult news. This is not easy. It's going to be hard for both of us. I need to let you know that we got the results of your test back.* [pause] *As we had feared, the lump is a malignant tumor, cancer.*

Once bad news has been given, we suggest that physicians say they are sorry. We do not use this word in the sense of taking responsibility for the bad situation or apologizing for it, but rather to express sympathy and regret. It is often appropriate to respond on a human level, such as reaching out and touching the patient. It is acceptable to cry if feeling especially sad about the news; patients will not see their physician as weak or unprofessional but simply as a caring human being. For example, the conversation above may continue as follows:

PHYSICIAN: *I'm sorry about this. This is very hard news to hear. Are there any questions that I can answer for you now? We will be discussing this more in the next week.*

TABLE 1.—*Principles of Communicating Bad News*

Choose a quiet setting
Give the news in person
Choose a moment when patient and physician are rested and have adequate time
If an interpreter is used, talk to her or him in advance
Assess the patient's present physiologic and emotional state
Prepare the patient by saying there is a difficult topic to discuss
Use clear, simple language
Express sorrow for the patient's pain; be human
Give limited information; schedule time to talk again later
Be realistic; avoid the temptation to minimize the problem, but don't take away all hope
Explore how the patient feels after receiving the news
Reassure the patient of the continued availability of care no matter what happens

PATIENT: What does this mean? What do we do next?
PHYSICIAN: *We know this is very serious. Unfortunately, we don't know exactly how rapidly it will progress. For now, we need to run one more test that I will schedule, if you agree. You and I will keep talking about this as we know more.*

In choosing what to say first, the physician should avoid the temptation to give the patient too much information once the bad news has been delivered. Initial anxiety often blocks out everything else. A gradual process of changing the view of oneself and the future is better than attempting abrupt adjustments. Information should be spaced over several visits. The physician might say, "I know this is confusing; we can talk again tomorrow so that I can answer all your questions." When the discussion is taken up again, a careful assessment can be made of what has been retained; the physician should not be surprised if there were misunderstandings.

We recommend that physicians attempt to explore how a patient feels after receiving bad news and the reasons behind the feelings. The patient may say, "Just don't tell me I have AIDS. . . . " Ascertain the patient's conception of what it means to have the diagnosed disease or condition. Frequently the patient will relate a story of someone he or she knew or heard about with the condition, and specific fears may be elicited. Common fears, such as fear of pain, might be anticipated. We recommend that these concerns be validated, perhaps by simply saying, "I hear your worries about suffering." The physician might then decide which of these issues can be addressed and resolved at the moment and which can be dealt with later. Acknowledging personal and professional limitations here is crucial. For instance, pain can be managed by the physician with the assistance of nurses and pharmacists; a social worker might deal with disability issues, a member of the clergy with worries about death.

When talking about the prognosis of a terminal disease, physicians must become comfortable with uncertainty. Be hopeful without falsely leading patients on. For example, say, "This is a progressive disease, but we will certainly do what we can for you." Some estimate of remaining time is often important for planning, but the patient or family should be made to understand that it is impossible to be sure of the accuracy of such estimates. Physicians need to be aware of the tendency to err on the side of optimism when predicting the course of fatal diseases. Functional status is often a better predictor than pathologic staging in determining time remaining. Offer to keep the patient informed as changes occur or to help him or her recognize changes. Patients should be reassured, if possible, that they can contact the physician when things arise that are frightening. The patient will feel comforted knowing that their practitioner will be available no matter what events unfold.

What the patient has been told and how the patient reacts should be communicated to the nursing staff as soon as possible so that others can be prepared to offer emotional support and understand possible reactions, such as tears, anger, sleeplessness, or an increase in pain. A delay in communicating bad news to a patient can place nurses in a difficult position in their own relationship with the patient or family.

In summary, the effect of delivering bad news to patients can be improved by considering factors such as the setting, the timing, and the words used (Table 1). These principles can serve as a general guide. Specific situations, such as

knowing a patient well, may call for a different approach by the physician. Similarly, each physician will develop his or her own style for delivering bad news.

Communicating Bad News to Family Members

When it becomes necessary to notify family members of bad news, such as a death, the same principles of choice of setting and timing apply, as well as the advisability of stating the facts in a clear, simple manner. Again, physicians should say they are sorry the family must suffer this loss. Family members are probably not greatly interested in the technicalities of the death. Comforting information, however, can be useful. For instance, the physician might say, "I [or the nurse] was with your husband when he died. He looked peaceful and did not suffer." Technical details may be in order later, after the emotional impact has subsided.

Problems in Delivering Bad News

One problem that can arise when bad news is delivered is denial on the part of the patient or a family member. This denial can be extreme and may reach such proportions that the person can be considered delusional. Denial should be understood to mean that the truth feels too painful or too threatening to assimilate at this time. If the patient continues to cooperate with treatment, a period of denial may not be problematic. We recommend that the physician maintain the bond with the patient, who needs help desperately, while gently and slowly attempting to develop the patient's awareness. The patient should be asked how he or she understands what is happening. If the patient denies reality, the physician might ask if there may be a time when he or she might consider another explanation. The physician should keep assessing how the patient is coping, perhaps by saying, "How do you feel things are going?" With time, and perhaps with the progression of the disease, most patients and family members can bear to hear bad news.

Another problem that may arise when communicating bad news is a request for collusion to hide the news. Such a request may come from either the patient or the family. The request may be culturally based; in some societies it is traditional for older persons to give up decision-making powers to younger family members. It is important to realize that the request to hide the diagnosis or prognosis is usually made out of love, not out of denial of the seriousness of the situation. It is useful to acknowledge this, and then explore the reasons given for the request. Physicians often hear concerns that the other will "fall apart" or "just turn her face to the wall." In addition, when the condition may have a societal stigma, as with AIDS or even cancer, shame or guilt may play a role. A strategy that may be helpful in this situation is for the physician to present as an expert who knows that people want to be informed about their condition, or the condition of a loved one, even if it may be difficult, so that they can plan for the future, vent emotions, and take care of business. The person who has not been informed often "knows" anyway but is afraid to talk openly in the family. Serious illness is a time of change, physiologically, psychologically, and socially. Even when the physical changes are destructive, the psychological and social changes may be constructive, and some of the gratification in caring for the seriously or terminally ill comes from facilitating this positive change in patients and families.

A useful strategy for dealing with problems that arise while needing to deliver bad news is to enlist the aid of other health care professionals. Often nurses or social workers become particularly close to patients and family and can be helpful during the process of acceptance that must occur. By discussing the situation with the other health care workers before talking to the patient or family, others can deal with their own feelings and be supportive to the patient.

Physician Responses to Communicating Bad News

Communicating bad news can be difficult. The physician may have feelings of impotence, or even guilt or failure: "If only I'd done that mammogram/stool guaiac/Pap smear/got him to stop smoking." Some physicians attempt to block off their own feelings to be spared the continued pain of dealing with these sad situations. Unfortunately, this often results in the patient and family feeling bad as well as the physician feeling resentful, distant, and unfulfilled. We recommend that practitioners acknowledge and talk about their own involvement in these situations. Using the methods and strategies outlined in this article can transform these intense interactions from stressful, unpleasant confrontations into meaningful communications. The physician may be seen as representing the good things about humanity to the patient and family, helping them feel less alone at a difficult time. When responding in this manner, the physician may feel temporarily sad but also renewed.

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Editorials

Indoor Radon—What Is to Be Done?

ELSEWHERE IN THIS ISSUE of the journal, Samet reviews some of the current approaches for assessing indoor radon exposure and the associated risks for developing lung cancer.[1] It is not surprising that this topic is received with considerable interest. If, as he concludes, 10,000 to 20,000 cases a year of lung cancer result from indoor radon exposure, this is certainly a serious ecologic problem. If true, the significance of this assertion is critically dependent on the degree to which the radon-induced cases are preventable. If they were all preventable, the potential effects on lung cancer mortality would be dramatic. Because the overall five-year survival rate for lung cancer is only about 10%, eliminating all radon-induced lung cancer would be comparable to a 100% increase in the theoretical five-year survival (calculated by comparing the five-year survival of a population that includes persons with exposure to radon and a similar population in which the radon exposure has been eliminated).[2] Unfortunately, as with most things in life, things are not as simple as they might seem.

In this review, a number of assumptions are made that appear to be reasonable and straightforward on the surface but may leave readers with a distorted perspective of what the practical implications are. Extrapolating indoor radon risk from that of radon exposure in miners is generally based on the assumption that there is a linear-no threshold relationship between radiation exposure (radon) and carcinogenesis (induction of lung cancer). Implicit in this theory is the dose-rate independence of the biologic effects of radiation. Several recent studies provide convincing evidence that the relative risk of radon-induced lung cancer is, in fact, not independent of the dose rate.

Hornung and Meinhardt, for example, found that among a cohort of uranium miners, low exposure rates were more harmful per unit of cumulative exposure than high-dose rates.[3] Similar findings were more recently reported by Lubin and co-workers and supported in an analysis by Darby and Doll.[4,5] A formal test of the linear-no threshold theory of carcinogenesis was reported by Cohen[6] who, using data from 411 counties from various parts of the United States, reported a negative correlation between radon exposure and the risk of developing lung cancer. The failure to confirm the validity of the linear-no threshold theory in this study may reflect the fact that low-rate radon irradiation is a more efficient inducer of lung cancer. If the dose rate is as important a factor as the total dose is for predicting cancer risk, an analysis that compares risk by dose (ignoring dose rate) might find a negative correlation. In any event, the available data suggest that the relationship between radon exposure and subsequent lung cancer risk is complex and not simply linear.

The significance of these dose-rate effects has major implications, particularly in light of the distribution of rates of exposure in the general population. Radon exposure rates in single-family homes follow a log-normal distribution skewed so that the vast majority of homes have low exposure rates.[7] Because low-dose rate exposure is more efficient at inducing lung cancer and because the vast majority of households have low rates of exposure, it follows that the vast majority of radon-induced lung cancers probably result from relatively low-dose rate exposures. Attempting to remedy this problem by identifying the small percentage of persons with exposure to relatively high-dose rates is not likely to be cost effective nor to result in a substantial reduction in lung cancer-related mortality.[8] The cost of a national effort to uniformly reduce indoor radon exposure could be considerable. For example, if, as proposed by some, the indoor radon levels were reduced to those found in outside air, the estimated average cost to homeowners would be approximately $10,000 each.[9]

The most cost-effective way to reduce the incidence of radon-induced lung cancer appears to be to reduce the number of smokers (there appears to be some synergism between smoking and radon exposure).[9,10] Additional measures that might be considered include improving the ventilation systems in existing homes (particularly in parts of the country where risk has been identified) and modifying the requirements for the ventilation systems for new constructions. Educating the population to do simple things, such as avoiding the use of basements as major living areas and discouraging the improper handling of actinide-containing mineral collections displayed in living areas, are further examples of potentially cost-effective intervention.[11] If funds that could be spent on smoking cessation programs are diverted to reduce radon exposure, it is possible that the lung cancer rates might actually increase!

Samet's review of current approaches for assessing the risk of indoor radon exposure brings the issue to mind but raises more questions than it answers. As he suggests, despite some uncertainty, data obtained from radon exposure in miners appear to have provided valuable information for assessing the indoor risk. But in light of these uncertainties, what is to be done? Until proved otherwise, it appears that the most cost-effective way to reduce radon-related lung cancer mortality is to discourage smoking, to encourage good indoor ventilation, and to discourage other behaviors that are likely to result in higher exposures to radon gases.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Nervous About Ticks—Assessing Lyme Disease Risk in San Diego County

To THE EDITOR: The recent finding of a tick infected with the Lyme spirochete in Orange County near the San Diego County border has stimulated public interest and occasional hysteria (J. Webb, PhD, Orange County Vector Control District, oral communication, June 1991). To assess the probability of acquiring Lyme borreliosis in San Diego County, in November 1990 we began screening those areas reportedly high in tick numbers or anecdotally associated with case reports of Lyme borreliosis. Tick sampling for questing adults was done by dragging or flagging.[1]* Habitat with appropriate vegetation and animal reservoirs was emphasized. Sites yielding high numbers were revisited about once a month during the cool season. Adult specimens of the Western black-legged tick, *Ixodes pacificus*, a known competent vector of *Borrelia burgdorferi*, were readily obtained (n = 1,046). These often locally outnumbered the cumulative tally of other tick species present, including the Pacific Coast tick and the American dog tick (*Dermacentor occidentalis* and *Dermacentor variabilis*). We individually dissected 250 adult *I pacificus* (both sexes) from nine identified collection sites around the county for midgut darkfield examination and direct immunofluorescence staining (method verified with R. S. Lane, PhD, Department of Entomological Sciences, University of California, Berkeley, oral communication, March 1991. Monoclonal antibody was obtained from A. G. Barbour, MD, PhD, University of Texas Health Science Center at San Antonio, written communication, February 1991. Tick specimens were verified by R. E. Monroe, PhD, College of Sciences, San Diego State University, as consistent with *I pacificus* Cooley and Kohls, oral communication, June 1991). Among these we found none infected with *B burgdorferi*. From this work we can infer, with $\alpha = .05$ and 90% power, that the current overall San Diego County infection rate in competent tick vectors is less than 4% (one-sided test), compared with estimates of overall prevalence at sites in northern California of 1%.[1]

We conclude that a competent vector for Lyme disease is widely prevalent in San Diego County and is in some foci very numerous. With increased public penetration of wilderness areas, increased attention to a Lyme borreliosis health hazard is warranted. An ongoing program of monitoring vector and reservoir populations seems prudent considering the factors of rapid development and human encroachment on vector habitat.

*Carrie Fogarty, Nancy Scarduzio, and James D. Lang, PhD, assisted in collecting ticks. A. S. Benenson, MD, provided methodologic advice.

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A Medical Practice Opinion Program

To THE EDITOR: I read with considerable interest the article in the August 1991 issue on the perils of providing medical opinion.[1]

I think there is a need for this type of program and that even though the economic risks are considerable, the program should continue. The California Medical Association ought to reactivate the Medical Practice Opinion Program and either assume the liability and economic consequences or direct that the requests for medical opinion be funneled through the Medical Board of California.

As a medical practitioner and observer of the many medical, political, and economic issues in our society, it is my opinion that if this program is not reactivated and if physicians, hospitals, and medical societies are not willing to express a reasoned and well-thought-out opinion, there will be increasing pressures to allow marginal medical and pseudo health procedures to be perpetrated upon the public. I am already observing the rise of certain marginal procedures and marginal indications for procedures that years ago never would have occurred.

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REFERENCE

1. Williams HE, Ramsey LL: The perils of providing medical opinion—A state medical association's experience. West J Med 1991 Aug; 155:183-185

* * *

To THE EDITOR: I am writing to comment on the article entitled "The Perils of Providing Medical Opinion" in the August 1991 issue.[1] It seems to me that this is a highly worthwhile function performed by the medical association and one that should be continued at all cost. The cost of litigation cited in the article seems low in view of the public service provided and particularly in view of the size of the membership supporting this activity.

The solutions suggested certainly should be pursued, particularly those seeking immunity from prosecution through legislative action and those continuing the program at full activity, even if this requires further financial support from the membership.

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* * *

To THE EDITOR: The article in the August 1991 issue entitled "The Perils of Providing Medical Opinion"[1] caught my eye. It was so lucid and cogent that it stimulated thought.

Under possible solutions, let me suggest either a new one or perhaps a modification of your third alternative—the one to funnel all requests through the Medical Board of California. What seems to be needed is an expression of legislative intent or perhaps legislative action that recognizes the great public health benefit of unfettered professional opinions.

Why doesn't the California Medical Association work with the physician members of the legislature to introduce legislation that would require the Medical Board and the Department of Consumer Affairs to sample expert professional opinion on issues at the growing edge of medicine. It would be the further responsibility of the Medical Board or the Department of Consumer Affairs to publish these opinions in the public interest.

A vital piece of the new legislation would be that the Department of Consumer Affairs or the Medical Board be empowered to contract with long-established, viable, and representative professional organizations to provide the technical and clinical bases for opinions.

This is, of course, the germ of an idea only, but at least it is an attempt to reactivate the Medical Practice Opinion Program and at the same time protect it from capricious or venal suits.

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Mistreatment of Gay Medical Students

To the Editor: I read with great interest the report by Dr Baldwin and colleagues concerning medical students' perceptions of mistreatment during their training.[1] Several areas of abuse were discussed, including humiliation, threats of physical harm, actual physical violence, and sexual, as well as racial, harassment.

There exists another form of sexual abuse, however, that was not specifically mentioned in this very well-written and thoroughly researched paper—the abuse perpetrated on gay and lesbian medical students by some members of faculty, medical staff, nursing staff, resident physicians, and peer student groups.

One type of abuse is the general and practically universal blindness of the medical profession toward the existence of gay physicians and medical students. Although many would deny their existence, gay health professionals clearly exist.[2,3] The conspiracy of silence and the unwillingness to acknowledge the presence of gays in medicine make it virtually impossible for a gay medical student to have access to gay role models. Many gay faculty and staff physicians do not feel comfortable about revealing their gayness because of potential reproach or hostility from peers or authority figures. I know this because of my own gayness.

Physicians and other health professionals have been shown to harbor very negative attitudes towards gay medical students and gay physicians.[4,5] These negative and prejudicial feelings are occasionally openly demonstrated, often in the form of a "joke," at which the gay or lesbian medical student may feel compelled to smile. Gay health professionals may be exposed to homophobic snide remarks, snickers, and derogatory comments and gestures. These I have personally encountered, a result of which I have felt hurt, anger, resentment, fear, humiliation, and embarrassment; in short, I was abused.

Most people assume the heterosexuality of physicians, and some feel compelled to force heterosexual behavior upon them. One of my teachers made a vigorous attempt to persuade me to date a certain woman physician, to my utter humiliation and confusion. I do not date women and trying to make me do so is a form of sexual abuse.

Being a gay physician, I know how much it can hurt to hear people unjustly comment on a sexuality about which they actually know little. This bigotry is clearly a form of sexual abuse. Gay and lesbian medical students need not be subjected to these painful, ignorant, and biased forms of behavior from teachers, peers, or co-workers.

I am happy and proud of my gayness. I have revealed the fact that I am a gay pediatrician through my published work.[6] I will not be silent about the pervasive sexual abuse being done to gay and lesbian members of the medical profession, including our medical students, who are particularly vulnerable to this outrage.

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HIV Incidence in Nevada?

To the Editor: In their recent article summarizing the epidemiology of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) in Nevada, Jarvis and Semiatin state there were 737 new HIV "seroconversions" during the first 12-month period (beginning July 1988) in which laboratories were required to report positive HIV test results, with an additional 100 "seroconversions" reported each year from anonymous test sites.[1] The authors conclude that "Taken together, these statistics seem to indicate that Nevada is experiencing nearly a thousand new HIV infections each year."[1(p40)] We think the data presented are not sufficient to estimate HIV incidence.

The authors present HIV testing and seroprevalence data from laboratories, anonymous test sites, civilian applicants for military service, unlinked anonymous newborn testing, and mandatory screening of newly incarcerated prisoners. These data measure the number of HIV-infected people in each population at the time testing was done but do not indicate when HIV exposure or seroconversion occurred. Prevalent HIV infection estimates represent the sum of new infections occurring in past years minus the number of deaths and migrations out of the state. Thus, incident HIV infections in the most recent year may represent a relatively small proportion of the infections cited by the authors. In addition, seroprevalence estimates may be artificially biased upward because many unlinked seroprevalence studies and anonymous testing strategies cannot differentiate the number of unique seropositives versus the number of positive antibody tests. Finally, persons at increased risk for HIV infection may be more likely than persons at lower risk to seek publicly funded services where antibody testing may be available.

Estimating the number of new HIV infections during a

given year requires that dates of the last negative HIV test result and subsequent positive test result be ascertained. This is possible if a group of initially uninfected persons are retested at regular intervals.[2] These types of studies, however, are expensive. Statistical techniques are currently being developed to estimate incidence from serial point-prevalence studies of the same population but have yet to be rigorously tested.[3] It is also possible to obtain minimum estimates of HIV incidence from persons attending anonymous test sites if questions are included to ascertain the date of the last HIV-negative test and the date of the subsequent positive test.[4] Such estimates should also include an adjustment for those who retest after their initial HIV-positive result.

Given the biases presented earlier, estimates of new infections based solely on the data presented should be substantially less than 1,000. Even if HIV incidence among those populations tested were estimable, results would likely underestimate incidence because of the many asymptomatic HIV-infected Nevadans who have not yet been tested. Given that Nevada accounts for 0.4% of AIDS cases in the United States[1] and the nationwide estimate is 1 million people living with HIV,[5] there may be over 4,000 Nevadans who are HIV-positive.

The incidence of HIV provides the most direct measurement of the spread of HIV, but accurate estimates are not easily obtainable. Seroprevalence and testing data provide more accessible but less direct measurements of disease spread and may provide information about HIV incidence in certain situations if used carefully.

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3. Sokal D, Shelton B, Kupper L: Calculating HIV incidence rates from seroprevalence data. Poster presentation at the Fifth International Conference on AIDS, Montreal, June 8, 1989

4. Reardon J, Parish M, Eaton R, et al: Estimated HIV-1 infection rates in Contra Costa County, California, 1990. Poster presentation at the Fourth National AIDS Update Conference, San Francisco, May 19-22, 1991

5. Centers for Disease Control: HIV prevalence estimates and AIDS case projections for the United States: Report based upon a workshop. MMWR 1990; 39(RR-16):1-31

* * *

Dr Jarvis Responds

To the Editor: Singleton and colleagues correctly state that the data presented in the recently published brief article concerning AIDS and HIV infection in Nevada[1] are inadequate for purposes of estimating HIV incidence accurately. As they briefly outline, attempts to estimate the incidence of HIV infection in populations are complicated by a number of possible biases, such as repeat testing of persons with positive test results, difficulties verifying unique test results in unlinked or anonymous testing programs, and the potentially lengthy asymptomatic lead time after seroconversion. The efforts to overcome these problems so that HIV incidence rates can be more accurately estimated are appropriate. Whatever the true incidence of HIV infection is in Nevada, the increasing AIDS incidence rate and the continued spread of HIV infection among Nevadans should compel the attention of state policymakers to public health measures likely to reduce future HIV-related morbidity and mortality.

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Thyroid Dysfunction and False Pregnancy

To the Editor: I read the recent interesting report by Drs Caudill and Lardinois on thyrotoxicosis and psychosis.[1] Psychiatrists have long been aware of the changes in mental state associated with thyroid dysfunction.[2] Somatic complaints are also frequently described by patients in addition to changes in mood, cognition, and sensory perception. I was struck by the description of Drs Caudill and Lardinois's patient's particular fear of being pregnant (she was sexually active, although no other reason for her fears were reported). I recently reported two cases of delusional pregnancy (or, as I dubbed it, "pseudo-pseudocyesis") in patients with manifestations of Hashimoto's thyroiditis and hyperthyroidism ("Pseudo-pseudocyesis" and Hashimoto's Thyroiditis, *Northern California Psychiatric Physician* newsletter, September 1991, p 7). Both patients presented with delusional symptoms, including an unshakable belief in being pregnant. One patient had organic mania; the other was diagnosed with major depressive disorder.

The disruptive effect of thyroid disease on normal menstrual cycling is well recognized.[3] The changes in mental state with thyroid disease can lead to distortion and misinterpretation of reality.[1] Changes in catecholamine receptor density in the central nervous system, second-messenger adenosine 3′:5′-cyclic phosphate processes, and "false neurotransmitter phenomenon" may account for the psychiatric disturbances.[4] The amenorrhea or dysmenorrhea that may accompany thyroid disturbances in women could be misinterpreted as a pregnancy, particularly in patients with changes in mental state. It seems prudent to evaluate full thyroid functions in patients with false pregnancy, or pseudocyesis.

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Durable Power of Attorney for Health Care

To THE EDITOR: The article by Dr Goldstein and colleagues, reporting on the level of awareness among health care professionals of the Durable Power of Attorney for Health Care (DPAHC),[1] provides interesting information on a subject about which little is known. The limitations of this study need to be emphasized, however.

Although a cursory mention is made of the fact that advance directives have received an enormous amount of publicity during the years since the study was conducted, the authors nevertheless claim, in the present tense, that "health care professionals are ill prepared to inform patients about advance directives." This may have been true in 1988, when California's DPAHC statute was still relatively new, and while it is possible that it remains true today, the study at hand obviously cannot support such a conclusion. I question whether it supported this conclusion even in 1988, to the extent that the conclusion was drawn on the basis of responses from just 216 professionals affiliated with a single teaching institution—hardly a representative sample of all professionals in the state.

In view of the continuing educational efforts of professional organizations—including the California Medical Association, which initiated an educational program more than six years ago with the mailing of a booklet titled *What Physicians Should Know About Durable Power of Attorney for Health Care* to each of its 34,000-plus members—I am optimistic that professionals today are much better educated about advance directives than the authors of this study seem to believe. Implementation of the Patient Self-Determination Act, which requires health care facilities to educate their staffs about these issues, will further accelerate the process.

Finally, I would like to point out that the answer to one of the questions used to measure knowledge of the DPAHC, shown in Figure 1, is incorrect. The family physician, to the extent he or she is the patient's "treating health care provider," may *not* serve as the agent under a DPAHC.

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REFERENCE

1. Goldstein MK, Vallone RP, Pascoe DC, Winograd CH: Durable Power of Attorney for Health Care—Are we ready for it? West J Med 1991 Sep; 155:263-268

* * *

Dr Goldstein Responds

To THE EDITOR: Mr Purdy raises an important issue about the time-sensitive nature of information about health care professionals' awareness of the Durable Power of Attorney for Health Care (DPAHC). I agree that it is likely that California professionals have been made more aware of the DPAHC by a combination of factors, including the publicity that surrounded the Nancy Cruzan case,[1] the upcoming implementation of the Patient Self-Determination Act,[2] and the continued educational efforts of organizations like the California Medical Association. The typical long delay between initiation of a project and final publication is a well-known problem of clinical research. Our article made clear the time frame in which the study had been conducted. Medical readers must continually extrapolate from the data available to their present condition of knowledge and determine how best to apply the findings.

Mr Purdy states that the California Medical Association initiated an educational program more than six years ago. This would mean that our data collection took place three years after this educational effort was begun, making the finding of low levels of awareness of DPAHC even more important.

The major study findings remain significant. One important finding was that positive attitudes toward DPAHC were not accompanied by behaviors that would encourage its use. Another finding was that professionals who had experience with the use of the DPAHC had encountered some problems in its use; it is likely that this would increase rather than decrease as the DPAHC is used more commonly unless these problems are addressed by educational efforts. We also reported that the hospitals at which the study was conducted had in place policies regarding the use of DPAHC, yet many professionals were unaware of it. Thus, the presence of a written policy does not guarantee awareness of the DPAHC. Finally, even the professionals who were aware of DPAHC had a poor specific knowledge of it; thus, educational efforts or publicity that increase awareness of DPAHC may not ensure a full understanding.

I thank Mr Purdy for pointing out the incorrect answer given to question 10 in Figure 1, a mistake made when the questionnaire was retyped for the figure. The data were analyzed with the correct answer. It is important to note that the specific items of information about the DPAHC are also time-sensitive since the legislation has been updated several times. The questions in Figure 1 were provided to show the level of detail of questions used for the study. They were appropriate at the time of the study but should not be regarded as the current status of the law. Current information may be obtained from the California Medical Association, from the California Civil Code (Section 2500), or from an attorney familiar with this area.

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1. *Cruzan v. Director,* Missouri Department of Health, 110 S Ct 2841 (1990)
2. HR 5835, 109, §4206, 1990

Correction

The following references should have been included with the October 1991 Radiologic Case by Padmanabhan, Gadde, and Vora: "Acute Mediastinal Widening Following Endotracheal Intubation and Gastric Lavage."

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Michel L, Grillo HC, Malt RA: Esophageal perforation. Ann Thorac Surg 1982; 33:203-210

Lessons From the Practice

The Gift of Sight

ROBERT M. KERSHNER, MD, FACS, *Tucson, Arizona*

It was nearing the end of a long, hot, dusty day in the Navajo reservation in northwestern Arizona when a young Indian man stood shyly in the doorway of our makeshift eye clinic just as we were about to close our doors for the night. The young man explained that his great-grandmother wanted her eyes examined although she had never been to a doctor in her life. As a volunteer at the Arizona Medical Eye Unit, a project started in 1979 to provide ophthalmic examinations to the Indians of the Navajo reservation, I was aware that many Indians did not receive specialist medical care if they did not travel off the reservation.

He explained that she lived as many Navajo elderly did, with her family in a "hogan" or hut. Since he was a boy, and for the past 27 years he had known her, they had cared for her, clothed her, and fed her because she was blind. He walked to his truck and returned leading an elderly woman by the arm.

For me, in 1985, a young doctor from the city, she was a magnificent sight. Dressed in the traditional long black dress of the Navajo, she was wearing elaborate pieces of turquoise and silver jewelry, collected through years of trading between the various Indian groups of the region. One look in her eyes revealed that both her pupils were as opaque as the turquoise jewelry she wore. She had advanced cataracts. I told her great-grandson her sight might be restored by surgery, which could be done in Tucson, several hundred miles to the south.

A preoperative physical examination showed this 103-year-old woman to be in remarkably good health. With local anesthesia and with her great-grandson interpreting my instructions for her, a cataract was removed and an intraocular lens implanted.

The next morning, as the bandage was carefully removed, she looked at me and spoke a few pleasant-sounding words in Navajo. Her great-grandson translated that she "liked my beard." Hearing his voice, she then turned to her great-grandson and smiled. She knew who he was from the sound of his voice, but she had never before seen his face.

That evening, on my drive home, I took the long way through the foothills surrounding the city. As the sunlight reflected its colors on the mountains, I imagined seeing it all for the first time.

(Kershner RM: The gift of sight. West J Med 1992 Jan; 156:91)

From the Orange Grove Eye Surgery Center, Tucson, Arizona.
Reprint requests to Robert M. Kershner, MD, FACS, Orange Grove Eye Surgery Center, 1925 W Orange Grove Rd, Suite 303, Tucson, AZ 85704-1117.

Spastic Gait Without Clonus

PIERO MUSTACCHI, MD, *San Francisco, California*

Neurosurgery was the best teaching service of the hospital where I interned. The senior resident taught clinical neurology so well I almost forgave him for having to be at ward rounds at 6:30 in the morning. With varying degrees of success, he instilled in us the compulsion that guided his exhaustive clinical histories and all-encompassing neurologic examinations. His prowess, invariably corroborated by surgery, awed and disheartened us, considering how much we still had to learn.

Only once did his diagnostic acumen stump him. An elderly Italian janitor was admitted to hospital after a bad fall that had not rendered him unconscious but had resulted in severe, nonradiating mid-back pain. There was no obvious bone lesion. From a neurologic standpoint, the only abnormality he exhibited was a curiously spastic gait: he kept his feet fairly wide apart and walked essentially on his heels, his big toes pointing up.

The skin over his soles was thickly keratinized, and plantar responses could not be elicited, nor could any of their innumerable equivalents of which my resident was an undisputed master. Except for the patient's spastic gait and the marked extensor response of both halluces when his heels touched the floor, there was no other suggestion of a pyramidal lesion. The clinical picture was rendered more confusing by the absence of obvious sensory deficits. Even a myelogram had failed to identify a lesion.

After a few days, his pain had subsided and he wanted to be discharged. But utilization committees had not yet been invented and my resident was adamant: the diagnosis had to be clear and certain before the patient could leave the hospi-

(Mustacchi P: Spastic gait without clonus. West J Med 1992 Jan; 156:91-92)

From the Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco, School of Medicine.
Reprint requests to Piero Mustacchi, MD, Department of Epidemiology and Biostatistics, University of California, San Francisco, School of Medicine, San Francisco, CA 94143-0560.

tal. I tried to intercede in the patient's behalf only to be reprimanded: "You speak Italian; you better go back to him, get a really good history, reexamine him, and come back with the correct diagnosis. At that point, we shall decide about discharge." Despite the futility of that request (even two attending physicians had agreed that the clinical picture was too incomplete to allow localizing the lesion), for the umpteenth time I went through the motions of taking a history from an increasingly resistant and hostile patient.

His answers went from brief to monosyllabic and eventually were only barely audible grunts. Finally, terrorized by the resident's probable reaction to my incompetence, I asked the patient, "But how long have you been walking like that?" "Like what?" "Well, walking on your heels, with your big toes sticking up." "Oh, like that?" he said. "Any time I don't wear slippers and the floor is cold and dirty."

The patient was discharged.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

Poems

AUNT EMMA COLLECTED TEETH

at night
when the senile
were contained by
their roll-bars
and tie-downs

she would flit out

shadow down the halls
with her sewing
basket

collect their unmouthed
dentures from the
bedside water
glasses

like some pearls being shucked

those bare gums knew
tried to tattle

but all the nurses ever did
was confiscate her basket in the morning
and shuffle out
the teeth

to those minus them

never did get all
the bites right
they said

even after Emma died

SHERYL L. NELMS©
Fort Worth, Texas

DAMN IT RAY

Mary Jane rubbing
his dry spotted hand

'Damn it Ray I've told you
sixteen times I love you
Look at me!'

Knotting her brow
'How could he
forget a wife
of sixty three years'

Arousing tousled
whispering 'Oh hell Mary Jane
you know I love you'

ANN SIMS©
Ponte Vedra Beach, Florida

NURSING HOME

Here the walls are thin
as birthdays.
There are no distinctions.

Handsome soldiers fade
in frames of the same war.
Cards repeat each other's verses
in the same drawer.

When you look
everyone withdraws
like yesterday
like the light beneath the door.

Little comfort you are their nightmare
long after they are yours.

DANIEL C. BRYANT©
Cape Elizabeth, Maine

LETTER FROM A NURSING HOME:

Found Sonnet

Yesterday they brought in a big
container of chickens
or eggs
ready to break open.
Well, for those raised on a farm
it wasn't too exciting
but I had never seen them.
Right out of the shell, their coat is strings.
Then we put them in a warmer
box or
cage and in three hours
those strings turned to fuzzy hair.
It was nice to see
even though farming doesn't appeal to me.

PHILIP DACEY©
Lynd, Minnesota

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Letters to the Editor must be double-spaced and will be published at the discretion of the Editors. They may be edited for style and brevity. Those of a scientific nature may be subject to peer review. They should be no more than 500 words in length. Authors will be sent galley proofs before publication.

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All references should be cited in the text and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in *WJM* style per the examples given below.

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Journal Articles

Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456
2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

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3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)
4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

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6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983
7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year).

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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(Continued from Page 23)

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This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

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February 2-9—**Office-based Sports Medicine—9th Annual Symposium.** University of California, San Francisco, School of Medicine, at Tamarron Resort—Purgatory Ski Area, Durango. One week. Contact: Extended Programs in Medical Education, UCSF School of Medicine, Room LS-105. (415) 476-4251.

February 8-15—**Seventeenth Annual Vail Psychiatry Conference.** Rose Medical Center and University of Colorado School of Medicine at Lion Square Lodge, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 8-15—**Sixth Annual Duke Symposium on Dermatologic and Rheumatic Diseases.** Duke University Medical Center at Marriott Mark Resort, Vail. One week. Contact: Symposium Coordinator, Duke University, (800) 457-1125.

February 8-15—**Fourteenth Annual Vail Emergency Medicine Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 10-14—**Family Practice Review,** University of Colorado School of Medicine, Denver. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 14-16—**Advanced Laparoscopy for the General Surgeon.** Rose Medical Center and University of Colorado School of Medicine at Loew's Giorgio Hotel and University of Colorado Health Sciences Center, Denver. Fri-Sun. Contact: David R. Scott, (800) 525-5810.

February 15-22—**Eighteenth Annual Vail Obstetrics and Gynecology Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 15-22—**Seventeenth Annual Vail Internal Medicine Conference.** Rose Medical Center and University of Colorado School of Medicine at Lion Square Lodge, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 22-29—**Seventeenth Annual Vail General and Vascular Surgery Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 22-29—**Neurology for the Primary Care Physician.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 28-March 2—**Principles of Anesthesia Technology.** University of Colorado School of Medicine at Marriott Mark Resort, Vail. Fri-Mon. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 29-March 7—**Colorado Review of Anesthesia.** University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 29-March 7—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

(Continued on Page 96)

(Continued from Page 95)

February 29-March 7—**Third Annual Vail Infectious Disease Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 29-March 7—**Fourteenth Annual Vail Pediatrics Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 7-14—**Seventeenth Annual Vail Primary Care Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 7-14—**"Minding the Body, Mending the Mind": Influencing Health and Healing.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 7-14—**Fifteenth Annual Vail Cancer Treatment Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 14-21—**Fifteenth Annual Vail Urology Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 14-21—**Fourteenth Annual Vail Sports Medicine Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 16-19—**Nineteenth Annual Neonatal and Infant Respiratory Symposium.** Ohio State University Hospitals at Marriott Mark Resort, Vail. Mon-Thurs. Contact: Arlene Rogers, Ohio University Hospitals, (614) 293-8487.

March 21-28—**Headache and Facial Pain Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 21-28—**Fourth Annual Colorado Geriatrics Overview/Board Review.** University of Colorado School of Medicine at Iron Horse Resort, Winter Park. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

IDAHO

February 21-23—**33rd Annual Medical Winter Clinics—Wilderness and Travel Medicine.** Ada County Medical Society at Shore Lodge, McCall. Fri-Sun. 9 hrs. Cat. 1. $100 for Idaho Medical Association members; $150, nonmembers. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

March 20—**Idaho Thoracic Society—Annual Medical Symposium.** St Alphonsus Regional Medical Center, Boise. Fri. Contact: Bill Smith, Program Director, Idaho Thoracic Society, 1111 S Orchard, Ste 245, Boise, ID 83705. (208) 344-6567.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 28-29—**20th Annual New Mexico Thoracic Society Lung Disease Conference.** El Dorado Hotel, Santa Fe. Contact: Billie Dytzel, 216 Truman, NE, Albuquerque 87108. (505) 265-0732.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

January 15-18—**Craniofacial/Oculoplastic Surgery** (Sponsor: UUSM). Wed-Sat. Snowbird. Contact: UUSM.

January 26-30—**Pediatric Critical Care Colloquium** (Sponsor: UUSM). Sun-Thurs. Snowbird. Contact: UUSM.

February 3-7—**Surgical Pathology** (Sponsor: UUSM). Mon-Fri. Park City. Contact: L. Larsen, (801) 581-5854.

February 9-14—**Interventional Radiology** (Sponsor: UUSM). Sun-Fri. Park City. Contact: Judy Gallegos, (801) 581-8188.

February 10-14—**Eleventh Annual Dermatology Seminar** (Sponsor: UUSM). Mon-Fri. Park City. Contact: Rosalie Lammle, (801) 581-8664.

February 14-15—**1992 Winter Ski Meeting** (Sponsor: Utah Ophthalmological Society). Fri-Sat. Prospector Square Hotel, Park City. Contact: Mark Fotheringham, (801) 355-7477.

February 14-18—**Syncope** (Sponsor: UUSM). Fri-Tues. Olympia Hotel, Park City. Contact: UUSM.

February 15-22—**Update in Clinical Microbiology and Immunology** (Sponsor: UUSM). Sat-Sat. Park City. Contact: Midge Beckman, (801) 581-7480.

February 17-21—**Pediatric Emergency Medicine** (Sponsor: UUSM). Mon-Fri. The Marriott, Salt Lake City. Contact: UUSM.

February 19-24—**Physical Medicine and Rehabilitation Update** (Sponsor: UUSM). Wed-Mon. Radisson Inn, Park City. Contact: UUSM.

February 20-21—**Protecting Your Right to Prescribe** (Sponsor: UUSM). Thurs-Fri. University Park Hotel, Salt Lake City. Contact: Sharon Thompsen, (801) 355-7477.

February 23-26—**The 32nd Annual OB/GYN Update** (Sponsor: UUSM). Sun-Wed. Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 26-29—**Infertility and Endocrinology Update** (Sponsor: UUSM). Wed-Sat. Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 28-Mar 3—**The 36th Anesthesiology Update** (Sponsor: UUSM). Fri-Tues. Snowbird. Contact: V. Larsen, (801) 581-6393.

March 2-6—**Microsurgery Workshop** (Sponsor: UUSM). Mon-Fri. University Park Hotel, Salt Lake City. Contact: UUSM.

March 8-14—**Advances in Internal Medicine** (Sponsor: UUSM). Sun-Sat. Snowbird. Contact: UUSM.

March 16-22—**Clinical Cardiac Electrophysiology Board Review** (Sponsor: UUSM). Mon-Sun. Snowbird. Contact: UUSM.

March 24-27—**Family Practice Refresher Course** (Sponsor: UUSM). Tues-Fri. Salt Palace, Salt Lake City. Contact: Leslie Munsee, (801) 581-7234.

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June 21-27—**School on Alcoholism, Drug Dependencies** (Sponsor: UUSM). Sun-Sat. U of U Browning Auditorium. Contact: UUSM.

June 24-27—**Slice of Life: Interactive Video and Related Multimedia Technology in Health Education** (Sponsor: UUSM). Wed-Sat. U of U Eccles Genetics Auditorium. Contact: UUSM.

July 12-17—**Update in Internal Medicine Focus on Ambulatory Care Medicine** (Sponsor: UUSM). Sun-Fri. Snowbird. Contact: UUSM.

August 6-8—**ISLD Dental Congress** (Sponsor: UUSM). Tues-Sat. Marriott Hotel. Salt Lake City. Contact: UUSM.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WRI: Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 16—**Law and Medicine Symposium.** Tacoma. Thurs. Contact: PCMS.

January 16-17—**Alzheimer's Update.** Seattle. Thurs-Fri. Contact: U/W.

January 24-25—**WTS Chest Conference.** Seattle. Fri-Sat. Contact: Washington Thoracic Society, (206) 441-5100.

January 31—**Vascular Surgery Update for Primary Care Providers.** Seattle. Fri. Contact: VMMC.

February 6-7—**A Day in the Office: Problems in Pediatric Practice 1992.** Seattle. Thurs-Fri. Contact: Group Health, (206) 326-3441.

February 7—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS.

February 14—**Cancer and the Nervous System.** Seattle. Fri. Contact: VMMC.

February 28—**Office Intervention: Alcohol and Substance Abuse.** Tacoma. Fri. Contact: PCMS.

March 9-13—**Geriatric Board Review.** Seattle. Mon-Fri. Contact: U/W.

March 9-19—**Physical Medicine and Rehabilitation.** Bellevue. Mon-Thurs. Contact: U/W.

March 12-13—**Internal Medicine Review—1992.** Tacoma. Thurs-Fri. Contact: PCMS.

March 20—**Integrated Approach to the Dizzy Patient.** Seattle. Fri. Contact: VMMC.

March 22-25—**Urgent Problems in Primary Care.** Bend, Oregon. Sun-Thurs. Contact: Group Health, (206) 326-3441.

March 23-26—**Death Investigations.** Seattle. Mon-Thurs. Contact: U/W.

March 25—**Ethics Conference.** Seattle. Wed. Contact: VMMC.

March 25-27—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health and Safety. (206) 543-1069.

March 30-April 3—**Hawaii and CME.** Kauai, Hawaii. Mon-Fri. Contact: PCMS.

April 10—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

April 10—**Gastro-Esophageal Reflux: A Multi-faceted Disease.** Seattle. Fri. Contact: VMMC.

April 17-18—**Tacoma Surgical Club.** Tacoma. Fri-Sat. Contact: PCMS.

April 24—**Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

April 24-25—**Diabetes of the Eye.** Seattle. Fri-Sat. Contact: U/W.

April 24-25—**Low-Back Pain.** Seattle. Fri-Sat. Contact: VMMC.

April 30-May 2—**Musculoskeletal Disease.** Seattle. Thurs-Sat. Contact: U/W.

May 8—**Office Procedures.** Tacoma. Fri. Contact: PCMS.

May 13-15—**Fifth Conference on Occupational Hazards to Health Care Workers.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health and Safety. (206) 543-1069.

May 21-22—**Cardiology Conference.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

May 27—**Pesticide Medicine.** Eastern Washington. Wed. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 30—**The Fetal Patient.** Seattle. Sat. Contact: VMMC.

June 22-23—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: PCMS.

June 26—**Sports Medicine.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

September 9-12—**Washington State Medical Association Annual Meeting.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 23-24—**Critical Care.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 11-13—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

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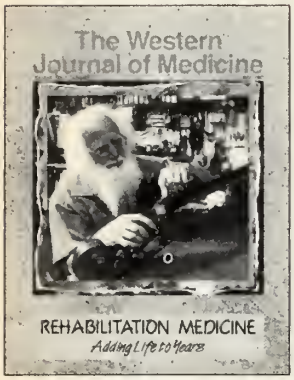

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- HIV INFECTION: IMPLICATIONS FOR REHABILITATION MEDICINE *Jon A. Mukand*
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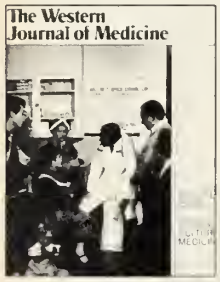
- PHARMACOLOGIC APPROACHES TO THE TREATMENT OF COCAINE DEPENDENCE *Wanda A. Taylor and Mark S. Gold*

Cross-cultural Medicine



M. Margaret Clark, PhD
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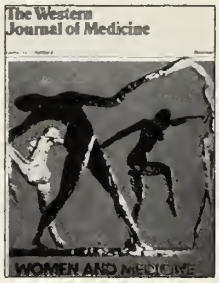

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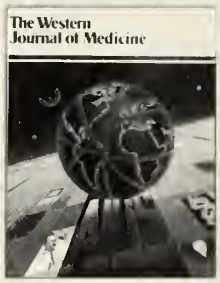

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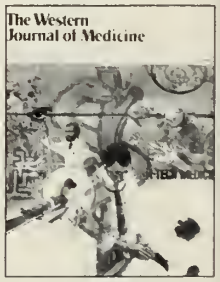

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MEDICAL DIRECTOR. FULL-TIME FAMILY PRACTITIONER, BE for new outpatient community clinic. Send résumé to Luisa Buada, Berkeley Primary Care Access Clinic, PO Box 11406, Berkeley, CA 94701-2406; FAX (510) 540-5742.

BC/BE FAMILY PHYSICIAN needed for large multispecialty group in San Jose, California. Family Practice Department. Includes Internal Medicine, Pediatrics, Gynecology, minor surgery with inpatient/outpatient responsibilities. Good call coverage exists. Competitive salary and benefits offered. Call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

MONTEREY BAY. Dynamic and cohesive medical community seeks Family Physician, Internist, and Pediatrician for group and/or independent practice. This is not a free lunch, but, in exchange for hard work, you'll be able to take time out to bike, surf, sail, climb, or supplement your education. Quality 200-bed hospital has solid community support. Unpretentious community, great for family, friendships, and lifestyle. For more information, please contact Ken Baker, President, at (415) 399-8840, or write Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; FAX (415) 781-7410.

TACOMA. Independent or group practice opportunity available to Family Practitioner or Internal Medicine physician with emphasis on Geriatrics. Tacoma, ranked as fourth best city in the US, and nearby Gig Harbor, are ideal communities for family, sailing, and outdoor lifestyle. This affordable area is still being discovered and the rewards of medical practice are alive and well. For more information, please contact Ken Baker, President, at (415) 399-8840, or write Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; FAX (415) 781-7410.

(Continued on Page 100)

Physician Executive

CIGNA Healthplans of CA is accepting applications for the position of Chief of Staff of several of its Health Care Centers. These Centers are part of CIGNA's 350,000 member Health Maintenance Organization in Los Angeles.

The Chief of Staff is the senior manager of the Health Care Center and has some clinical as well as administrative responsibilities.

Candidate qualifications are Board Certification, CA licensure, recognized achievement in management and reputation for clinical excellence. Additionally, the physician must be open-minded, option-inventing, innovative, action-oriented and have talent for motivating people.

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Contact: **Joseph W. Spooner, MD, M.B.A.**
Regional Medical Director
CIGNA Healthplans of CA
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Glendale, CA 91203
Phone: 818-500-6348
Fax: 818-500-6986
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(Continued from Page 99)

PHYSICIANS WANTED

NEPHROLOGIST WANTS PARTNER/ASSOCIATE BC/BE Gastroenterologist/Cardiologist/Nephrologist/Pulmonologist. Excellent practice, equal partnership opportunity without buy-in or overhead. Send CV to Dr M. Streger, 27800 Medical Center Rd, Ste 122, Mission Viejo, CA 92691.

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full-/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

ASSOCIATION AVAILABLE in semi-rural town, one hour from Seattle and one half hour from Tacoma. OB optional. Growing community close to mountains and Puget Sound. Owner to retire in three to four years. Contact D.A. Tait MD, Inc, PS, PO Box 164, Buckley, WA 98321; (206) 829-1444.

CALIFORNIA. Physician Recruiting Services available to solo practitioners, single and multispecialty clinics, and hospitals. Placement positions available in Invasive Cardiology, Family Practice, Dermatology, Ophthalmology, Internal Medicine, OB/GYN, Orthopedic Surgery, Neurology, General (Vascular) Surgery, Pediatrics, Urology, and others. For information call Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (510) 376-0762.

INTERNIST/FAMILY PRACTITIONER—Northern California. Immediate opportunity for BC/BE Internal Medicine/Family Practice. Practice associate emphasized or solo practice. Located north of San Francisco in wine country with outdoor activities. Assistance available for relocation and establishment of practice. Contact Margaret Ward, Redbud Community Hospital, Box 6720, Clearlake, CA 95422; (707) 994-6486.

PHYSICIANS WANTED

NORTHERN CALIFORNIA

San Jose's leading multispecialty group is growing. We are seeking BE/BC physicians in the following specialties:

- Urgent Care
- Family Practice
- Physiatry
- Otolaryngology
- Orthopedics

If you are committed to excellence and strongly motivated for success, we would like to hear from you. Please send your CV to Maureen Forrester, San Jose Medical Group, Inc, 45 S 17th St, San Jose, CA 95112; **or call (408) 282-7833.** Affiliated with Stanford University School of Medicine.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Linda Johnson, 8009 S. 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

BC/BE FAMILY PRACTITIONER, OB-competent, for nonprofit community clinic in California redwood country. Rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

INTERNIST. Immediate opening. Large, established, rapidly growing Los Angeles medical facility. High salary. Full benefits. Malpractice insurance paid. Contact Mr Miller; (213) 384-2504.

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SACRAMENTO URGENT CARE. Kaiser Permanente has openings for BE/BC Primary Care physicians for 30 to 40 hour positions in our busy adult Urgent Care centers. Full benefits available. Wide range of outpatient skills required. Prior outpatient experience is desirable. Option for some inpatient work. Daytime and weekend shifts allow some flexibility in scheduling. Contact Stuart Hahn, MD; (916) 973-5546, or request application from Carolyn Whelan, Physician Recruiting, The Permanente Medical Group, Inc, 2025 Morse Ave, Sacramento, CA 95825. EOE.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

INTERNIST BE/BC. Superior opportunity for Internist within a growing innovative group. Be a part of a progressive growing group providing care in the San Gabriel Valley. Competitive salary and full benefit package available to qualified candidate. Please send CV to Shirley Dykes, Arroyo Seco Medical Group, 800 S Fairmount Ave, Ste 110, Pasadena, CA 91105.

(Continued on Page 101)

(Continued from Page 100)

PHYSICIANS WANTED

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled, Family Practice or Emergency Physician to join highly respected Urgent Care group with two beautiful Santa Cruz clinics. Committed to high quality care. Nice people, flexible scheduling, comprehensive benefits, including paid malpractice, group health insurance, long-term disability insurance, no nights, rapid advancement to full partnership in an outstanding place to live. Please send CV to Stuart Simon, MD, 6800 Soquel Dr, Aptos, CA 95003; or call (408) 662-3611.

THE UNIVERSITY OF CALIFORNIA, San Francisco and the Central California Faculty Medical Group seek a staff Cardiologist to join the teaching faculty at their affiliate, Valley Medical Center of Fresno. Applicants should be BC/BE. Full invasive and noninvasive cardiology services are available. In addition to the academic participation, there is potential for private practice experience. Geographic location offers a large population with a variety of cardiological disease. VMC has 350 active beds and conducts residency training programs in most major clinical disciplines as well as a fully accredited cardiology fellowship. The central California location offers enjoyable and affordable California living. Competitive salary and benefits. UCSF is an equal opportunity employer. Address inquiries to Lauren Grayson, MD, Chief of Cardiology, CCFMG, 4910 E Clinton, #101, Fresno, CA 93727.

ORTHOPEDIC SURGEON. University of California, San Francisco seeks a BC/BE Orthopedic Surgeon to fill a faculty/staff position at the Valley Medical Center, Fresno. The Orthopedic Department at VMC supports a busy trauma service and actively participates in teaching residents in General Surgery, Emergency Medicine, and Family Practice. This position also offers private practice opportunities in a setting within the faculty group. Competitive salary and benefits. The central California location offers affordable and enjoyable year-round recreational living. Address inquiries and CVs to Louis Conway, MD, Acting Chief of Orthopedics, 4910 E Clinton, #101, Fresno, CA 93727. EO/AA employer, women and minorities are encouraged to apply.

FAMILY PHYSICIAN—SAN FRANCISCO BAY AREA. Small Family Practice group in Alameda seeks BC/BE Family Physician to join thriving practice. No OB. Contact Peter Candell, MD, Alameda Family Physicians; (510) 769-9492.

WARM AND SUNNY ARIZONA. Thomas-Davis Medical Centers, an expanding multispecialty group of 170 plus physicians, needs Internal Medicine, Family Practice, OB/GYN, Urgent Care, General Surgery, Orthopedic Surgery, Allergy, Dermatology, and Retina specialists. Top benefits, profit sharing, guarantee first two years, plus incentive pay, early shareholder. Fee-for-service plus HMO. BE/BC. Call or write Bill De Long; (800) 658-9166, TDMC, PO Box 12650, Tucson, AZ 85732.

PALO ALTO, CALIFORNIA. PART-TIME OR FULL-TIME BC/BE INTERNIST. Excellent opportunity for physician to become medical director of nationally recognized clinical facility specializing in the treatment of psoriasis and related conditions. Opportunities for research and establishment of private practice. Compensation package is competitive and based on the number of hours worked. Send CV to Jan Sturges, Medical Management Services, 532 Race St, San Jose, CA 95126.

PEDIATRICIANS—Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

BE/BC UROLOGIST to join busy 28 doctor multispecialty group practice. Excellent practice opportunity, full range of benefits, early partnership status. For more information contact Shane Spray, 1400 Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

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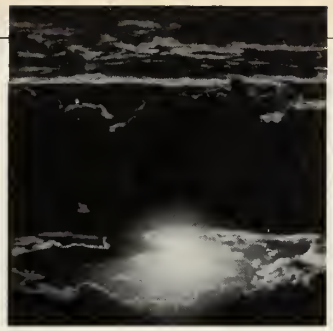

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The Division of General Internal Medicine, University of California, San Francisco, (UCSF), is hiring three General Internists to participate in the Division's clinical and educational programs beginning as early as spring 1992. Candidates should be BC/BE General Internists interested in an academic practice at a major academic medical center. The position involves 80% time in clinical practice the first year, changing to 70% in subsequent years. The remaining time is devoted to education of residents, medical students, and self. Candidates may develop a focus on women's health issues or in-patient medical consultation if desired.

The position offers a full range of benefits, competitive salary, and opportunity for academic advancement based on excellence in clinical medicine and teaching. Clinical faculty share equally in planning and policy-making for divisional programs, and will participate in the Division's educational programs.

Candidates should send CVs and a list of three references to:

Thomas McAfee, MD
Chairman, Search Committee
University of California, San Francisco
Division of General Internal Medicine
400 Parnassus Ave, Box 0320
San Francisco, CA 94143-0320

The University of California is an Equal Opportunity/Affirmative Action Employer. Women and minority candidates are encouraged to apply.

(Continued on Page 102)

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PHYSICIANS WANTED

PHYSICIAN: PRIVATE PRACTICE RENO/LAKE TAHOE, NEVADA

Pain Medicine physician specialist wanted for the Sierra Pain and Occupational Rehabilitation Center, a 15,000 square foot, CARF-accredited facility in **Reno, Nevada.**

Sierra Pain and Occupational Rehabilitation Center is a comprehensive, interdisciplinary pain management out-patient facility committed to excellence in care and clinical service.

Please send your CV and references to:
Richard J. Kroening, MD, PhD
Medical Director

Sierra Pain and Occupational
Rehabilitation Center
50 Kirman Ave, Ste 101
Reno, NV B9502

For more information, please feel free to call Administrative Director Jeannee M. Russell:
(702) 786-9779

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FAMILY PRACTICE, BC/BE to join group practice in growing southwestern town. Full service clinic, 280-bed hospital. Offering competitive salary, equal call schedule, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

PRIMARY CARE PHYSICIANS. Rewarding opportunities available for BC/BE Internists and Family Physicians to join a dynamic, quality driven, academic Ambulatory Care Program. Spend more time with your family as you work desirable hours while earning a generous salary and benefits. Our progressive management strives to enhance your professional satisfaction! No overhead, billing, or third party reimbursement hassles. Beautiful mountain community with four season recreational opportunities, little traffic congestion, and no state income taxes. Send CV to Kurt Schlegelmilch, MD, VA Medical Center, 1000 Locust St, Reno, NV 89520; telephone (702) 328-1286. Equal opportunity employer.

PALO ALTO, CALIFORNIA. PART-TIME OR FULL-TIME BC/BE DERMATOLOGIST. Excellent opportunity for physician to become medical director of nationally recognized clinical facility specializing in the treatment of psoriasis and related conditions. Opportunities for research and establishment of private practice. Compensation package is competitive and based on the number of hours worked. Send CV to Jan Sturges, Medical Management Services, 532 Race St, San Jose, CA 95126.

GENERAL SURGEON. Full-time BC/BE General Surgeon for multispecialty group in southeast Los Angeles. Office/hospital and consulting practice. Spanish a plus. Top salary, benefits, and malpractice insurance. Potential for shareholdership second year. Send CV to Craig Kaner, Administrator, All Care Medical Group, Inc., 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

OB/GYN. Full-time BC/BE OB/GYN for multispecialty group in southeast Los Angeles. Office/hospital practice. Spanish a plus. Top salary, benefits, and malpractice insurance. Potential for shareholdership second year. Send CV to Craig Kaner, Administrator, All Care Medical Group, Inc., 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

PHYSICIANS WANTED

CODY, WYOMING . . .

. . . has an immediate position available for a BC Emergency Physician. Live and work in the beautiful Rocky Mountain region, located only 50 miles from Yellowstone Park. Area abundant in fishing, hunting, and outdoor sports. NO STATE INCOME TAX! For more information call (307) 578-2488 or send CV to Gary Bishop, CEO, West Park Hospital, 707 Sheridan Ave, Cody, WY 82414.

BEAUTIFUL OREGON COAST. Private multispecialty cooperative with excellent facility seeking Family Practice physician to join five full-time Family Practitioners. Full spectrum of Family Practice. In-house lab, x-ray, day surgery. Contact Marce Knight, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294 or (800) 234-1231.

NEW MEXICO. Excellent opportunity for BC/BE OB/GYN, Internal Medicine, and Family Practice to join successful practices or start new in a growing community. Plan on full practice from the beginning. Enjoy sunshine, skiing, hiking, fishing, and hunting in a southwestern lifestyle. For further information on benefits and compensation contact Anne Winter, RN, Director of Professional Development, St Joseph Healthcare System, Albuquerque, NM; (505) 246-8003.

POSITIONS AVAILABLE FOR EMERGENCY PHYSICIANS WORKING PM SHIFTS. Hourly differential paid in addition to fee-for-service compensation. Shifts vary from seven to nine hours in length. Excellent fringe benefits. Malpractice paid. Contact Nancy C. Kendall at SPEMG, Inc, 5777 Madison Ave, #1090, Sacramento, CA 95841, or call (916) 974-3154 for more information.

BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

BC/BE GENERAL INTERNIST NEEDED. Nine physician department in 27 doctor multispecialty clinic. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

INTERNIST/FAMILY PRACTITIONER. Join progressive and well respected community clinic in desirable San Francisco/Oakland bay area. Position available for Internist or Family Practitioner with strong Internal Medicine background. Limited call, 3.5-5 day work week; salary plus fee-for-service for inpatient care. Excellent fringe benefits which include malpractice insurance. Send CV to Pat Royball, Personnel, La Clinica de la Raza, 1515 Fruitvale, Oakland, CA 94601; (510) 534-0078.

INVASIVE AND/OR NONINVASIVE BC/BE CARDIOLOGIST needed for well established private practice in Riverside, California. Salary guarantee. With partnership potential. Immediate opening available. Send CV to 3900 Sherman Dr, #B, Riverside, CA 92503, attn: Lynn.

INTERNAL MEDICINE. Internist, BC/BE, needed for well established private practice in Riverside, California. Salary guarantee. Immediate opening available. Send CV to 3900 Sherman Dr, #B, Riverside, CA 92503, attn: Lynn.

OPPORTUNITY for full- and part-time Emergency Physicians. Excellent fee-per-patient load ratio. Malpractice paid. Also, Emergency Department/Family Practice positions for urgent care/industrial center. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

PHYSICIANS WANTED

NORTHERN CALIFORNIA—SOUTH BAY

BC/BE Family Physicians and Internists needed for:
- large multispecialty group
- solo/small group practice
- Urgent Care setting.

All positions offer competitive compensation packages. For additional information please send CV to **Jan Sturges, Medical Management Services, 532 Race St, San Jose, CA 95126.**

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

FOURTH INTERNIST/FAMILY PRACTICE MD for well loved multidisciplinary health center part of east San Francisco bay area community clinic network. 24 plus clinic hours plus share hospital call and coverage. Resident teaching and UCSF clinical affiliation possible. Call (510) 644-6060.

WANTED: PHYSICIAN ADMINISTRATOR. NEW MEXICO. The Los Lunas Hospital and Training School, a 350-bed state operated facility for persons with developmental disabilities, is currently recruiting for a Physician Administrator. Located approximately 20 miles south of Albuquerque, New Mexico, we provide professional services and patient care to mentally and physically disabled clients. The job entails responsibility for general, technical direction of all service related to patient care and professional operations. Minimum qualifications include graduation from an accredited medical school and completion of an approved internship, plus four years experience in the practice of medicine, and licensure by the New Mexico Board of Medical Examiners. Salary up to $78,404 per year plus benefits; medical malpractice provided by the facility. Direct inquiries to David LaCourt, PhD, Administrator, Los Lunas Hospital and Training School, PO Box 1269; (505) 841-5264.

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The deadline for submitting classifieds for the March issue of WJM is January 24. Send your advertisement to:

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PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (510) 601-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

OCCUPATIONAL/FAMILY PRACTICE. The West coast's leading outpatient medical provider has opportunities for Primary Care physicians to join an expanding 150 person medical group. Full-/part-time openings throughout California and Seattle-Tacoma, Washington. Attractive package includes excellent base salary plus incentive program, malpractice insurance, comprehensive benefits, 401 (k) plan, vacation/sick/holiday/CME. Contact ReadiCare, Inc; (916) 363-6955, or send CV to attention Dennis Lowe, 9261 Folsom Blvd, Ste 400, Sacramento, CA 95826.

LAKE TAHOE FAMILY PRACTICE. Live in beautiful Lake Tahoe. Full-time position available in four physician practice. Position includes working half-time at an on-site Occupational Clinic in a large casino. Full benefit package. Contact or send CV to Darlene Vogds, Vice President of Operations, 9261 Folsom Blvd, Ste 400, Sacramento, CA 95826; (916) 363-6955.

MEDICAL CENTER SEEKS BC/BE INTERNIST with strong interest in Primary Care to join our University affiliated General Medicine section. Responsibilities include direct patient care, teaching, supervising, program development, and research. Academic appointment offered to qualified applicant. Send CV to Dr F. Kwiecinski (11C), VAMC, Tucson, AZ 85723.

SAN JOSE. Family Physician for a five physician Primary Care group. The practice is located within one hour of beaches, mountains and San Francisco, with nearby excellent 200-bed hospital. Salary plus incentives with partnership in two years. For more information, please contact Ken Baker, President, at (415) 399-8840, or write Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; FAX (415) 781-7410.

ANESTHESIOLOGIST, BC. Immediate half-time position in Pocatello, Idaho (50,000 population). Join four MDs and seven CRNAs. All specialties except Cardiac. Full benefit package. Excellent hunting, fishing, and skiing. Home of Idaho State University. Contact Philip J. Knox, MD; (208) 234-1363, 7727 Katsilometes, Pocatello, ID 83204.

OB/GYN. 100-BED, FULL-SERVICE HOSPITAL located 30 miles south of San Jose seeks a BE/BC OB/GYN to establish a solo practice due to area's growth. This is an outstanding opportunity for a physician wanting to establish his/her own practice. Call coverage is available and a competitive financial package is being offered. For further information, call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

OB/GYN—Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE Physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

TRINIDAD, CALIFORNIA

Private Indian clinic overlooking ocean on northern California coast seeking two BC/BE Family Physicians to join two other Family Physicians. Exciting, challenging, comprehensive program, including Obstetrics. Gael Dougherty, RN, Medical Department Coordinator, UIHS, PO Box 420, Trinidad, CA 95570; (707) 677-3693.

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The Western Journal of Medicine

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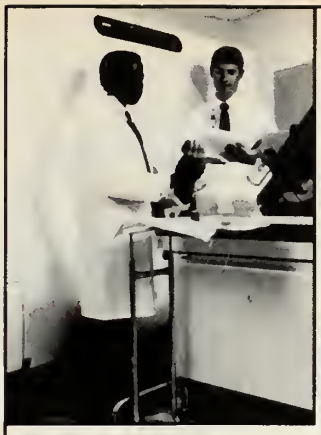

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"CIGNA Healthplan and I are a perfect professional match. They take care of administrative duties as well as malpractice insurance. And, I get to concentrate on the practice of good medicine."

"Now that I'm practicing with CIGNA Healthplan, I have more time to spend with my son...I'm even coaching his swimming team this year."

CIGNA Healthplan gives you the freedom to focus on what's most important...the practice of good medicine. We take care of the accounting, office management and more. And our locations offer you some of the best practice opportunities and lifestyles found anywhere. We currently have the following positions available:

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Pathologist
Pediatrician
Radiologist
Rheumatologist
Urgent Care

ARIZONA
Phoenix & Tucson

Anesthesiologists
Dermatologists
Diagnostic Radiologists (MRI, CT, Mammography, General Radiography)
Family Physicians
Internists
OB/GYNs
Occupational Medicine
Orthopedic Surgeons
Pediatricians
Urgent Care

As part of our team, you'll enjoy a predictable schedule. What's more, CIGNA Healthplan offers competitive salaries, comprehensive benefits, and the resources of a health care leader. For more information, call or send your CV to:

California: CIGNA Healthplans of CA, Professional Recruitment, 505 N. Brand Blvd., Suite 400-49, Glendale, CA 91203, (800) 468-9013.

Arizona: CIGNA Healthplan, Professional Staffing, P.O. Box 16145, Dept. 49, Phoenix, AZ 85011-6145, (800) 252-2471.

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(Continued from Page 103)

PHYSICIANS WANTED

WHERE BUT IN ALASKA could you expect to find the recreational dividends offered by this magnificent state?

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The Department of Veterans Affairs is currently recruiting technical and professional staff to fill positions for its new, modern ambulatory care facility.

Potential for vacancies in internal medicine, psychiatry, psychology, radiology, general surgery, urology, orthopedics, ophthalmology, otolaryngology and physiatry.

For information, write Personnel Service, 235 E. 8th Avenue, Anchorage, Alaska 99501 or call (907)271-2478.

Department of Veterans Affairs

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COLORADO. BC/BE INTERNIST to join three Internists in multispecialty group. Excellent opportunity for person interested in rural living, mountain recreation, health care for medically underserved population. Send CV to Marguerite Salazar, 204 Carson Ave, Alamosa, CO 81101; (719) 589-5161.

BC/BE GASTROENTEROLOGIST is needed to join a busy Gastroenterology practice in a rapidly growing community in California. Must be trained in therapeutic endoscopy. Reply to Number 253, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SALT LAKE CITY—URGENT CARE/FAMILY PRACTICE. Six year old center in upper middle class community. BC preferred, early partnership available. Great recreation area. Work Net, PO Box 26692, Salt Lake City, UT 84199.

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A FOUR PHYSICIAN OB/GYN DEPARTMENT of multispecialty group in San Jose, California seeks a fifth BC/BE OB/GYN to join their busy practice. Call schedule will be 1:6. Four-day work week. Competitive salary and benefits. Send CV to Jan Sturges, MMS, 532 Race St, San Jose, CA 95126-3432.

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CALIFORNIA OPPORTUNITIES. Multispecialty groups, hospitals, and private practices have engaged us to recruit for various openings in Family Practice, OB/GYN, Internal Medicine, Orthopedics, and Medical Directorships. Outstanding facilities in northern and southern California are seeking BC/Board Active candidates for high paying positions with excellent benefits. Contact Elaine Brand, Medical Consultants, 5700 Etiwanda, Ste 206, Tarzana, CA 91356; (818) 996-1524. No fee to physicians.

AMBULATORY CARE, Hayward—Modesto, California. Thriving practices, attractive facilities, competitive salary, profit-sharing, partnership with growth potential. Contact Robin Morgan, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612; (510) 835-7431. Outside of California, (800) 842-2619.

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SAN FRANCISCO. Full-time physician for busy Occupational Medicine clinic. Superb opportunity in rapidly growing clinic. Hospital affiliation, malpractice paid. Excellent support staff. Send CV to General Manager, IMS, 1580 Valencia, #202, San Francisco, CA 94110.

BE/BC INTERNIST sought with or without subspecialty interest to replace departing partner in busy seven member Internal Medicine practice ten miles south of San Francisco. Contact Diane Davis, MD; (415) 583-5352, 1001 Sneath Ln, San Bruno, CA 94066.

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(Continued on Page 105)

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(Continued from Page 104)

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OB/GYN—NORTHERN CALIFORNIA. Four person, single specialty group seeking recently trained US graduate. Send CV to Jack Rowland, 1400 Florida, Ste 205, Modesto, CA 95350.

SEATTLE, WASHINGTON. PACIFIC MEDICAL CENTER has Family Practitioner positions, BC/BE, available at three of its six neighborhood clinics. PMC is a growing, Primary Care-based, multispecialty organization with extremely well run, well equipped clinics that provide many ancillary services. Most of the clinics are located within one mile of a major hospital. PMC offers its providers a balanced life-style, competitive salaries, and an excellent benefit package that includes paid malpractice. The greater Seattle area offers year-round outdoor recreation including, skiing (snow/water), hiking, boating, and fishing at numerous lakes, national parks, and in Puget Sound. Send CV to Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4100.

EUGENE, OREGON. INTERNIST, BC/BE, to join well established 44 physician Primary Care group. Excellent schools. Abundant cultural and recreational opportunities. Near Cascade Mountains and coast. Home of University of Oregon. Please send CV to David Strutin, MD, Oregon Medical Group, 495 Oakway Rd, Eugene, OR 97401; or call (503) 342-2134.

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YELLOWSTONE NATIONAL PARK. Physician to cover Outpatient Clinic, Emergency Room, and inpatient at Lake Hospital from Memorial Day to mid-September 1992. Send CV to Yellowstone Park Medical Services, 707 Sheridan Ave, Cody, WY 82414, or call (307) 578-2461.

NATIONWIDE TRAVEL. Health research organization seeks physician for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individual will be part of a large medical team conducting health examinations in government mobile exam centers traveling to 88 areas of the US through 1993. Must be licensed in one state. One year minimum commitment and full-time continuous travel required. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline, (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD, EOE/M/F/V/H.

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URGENT CARE/PRIMARY CARE PHYSICIANS for over 90 positions available with various physician groups in Phoenix metropolitan/Tucson, Arizona. Excellent compensation and partnership opportunities. Contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

NORTHERN CALIFORNIA. BC/BE GENERAL INTERNIST sought in rural community. Solo practice with shared call schedule. Send CV to Number 257, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 106)

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SOUTHERN CALIFORNIA COASTAL COMMUNITY CARDIOLOGIST: BC/BE—invasive with angioplasty experience a requirement. Emergency Physician capability preferred—to join four person Cardiology group July '92. All members are BC, one invasive, three noninvasive. Please forward CV to Number 248, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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CALIFORNIA. The Lompoc Hospital District is recruiting a General Internist. Requires excellent communication and patient relation skills as well as BC/BE for certification. American training preferred. The District is facilitating a comprehensive and flexible compensation package including either a group or solo practice. The District provides a wide array of quality inpatient and outpatient services to a 50,000 resident service area through its well equipped, 60-bed acute hospital, 110-bed skilled nursing and urgent care facilities. Located between Los Angeles and San Francisco in scenic northern Santa Barbara county, Lompoc is surrounded by rolling hills and the Pacific coast shoreline. The community is family oriented and provides good schools and educational opportunities through the university level. In addition, the area supports outstanding recreational and cultural amenities. Exceptional housing opportunities exist at very affordable prices. Interested individuals should contact Scott Rhine, District Administrator, 508 E. Hickory Ave, Lompoc, CA 93436; (805) 737-3301.

CALIFORNIA. The Lompoc Hospital District is recruiting a Pediatrician. Requires excellent communication and patient relation skills as well as certification or eligibility for certification by the American Board of Pediatrics. American training preferred. The District is facilitating a comprehensive and flexible compensation package including either a group or solo practice. The District provides a wide array of quality inpatient and outpatient services to a 50,000 resident service area through its well equipped, 60-bed acute hospital, 110-bed skilled nursing and urgent care facilities. Located between Los Angeles and San Francisco in scenic northern Santa Barbara county, Lompoc is surrounded by rolling hills and the Pacific coast shoreline. The community is family oriented and provides good schools and educational opportunities through the university level. In addition, the area supports outstanding recreational and cultural amenities. Exceptional housing opportunities exist at very affordable prices. Interested individuals should contact Scott Rhine, District Administrator, 508 E. Hickory Ave, Lompoc, CA 93436; (805) 737-3301.

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CALIFORNIA MEDICAL/LEGAL DISABILITY EVALUATIONS. Opportunities available in San Jose, San Ramon, Fremont, and Capitola, California for BC physicians in Orthopedics, Psychiatry, and Cardiology with multispecialty forensic medical evaluation group. Practice limited to evaluations. California license required. Excellent opportunity to supplement income. Send inquiry and CV to Martie Woodson, QMA, 2131 The Alameda, San Jose, CA 95126.

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ONCOLOGIST WANTED. Oncologist wanted to join an Internal Medicine group in San Diego, California. Guarantee plus commission. Opportunity to join full partnership in two years. Number 250, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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PEDIATRICIAN—NORTHERN CALIFORNIA. BC/BE Pediatrician needed in foothill community. Excellent opportunity for private practice. Competitive income guarantee. Send CV to Number 256, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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(Continued on Page 107)

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(Continued from Page 106)

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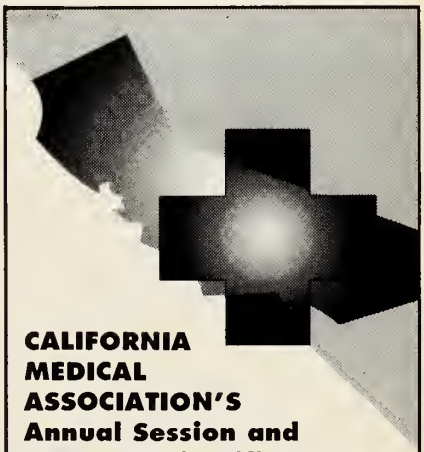

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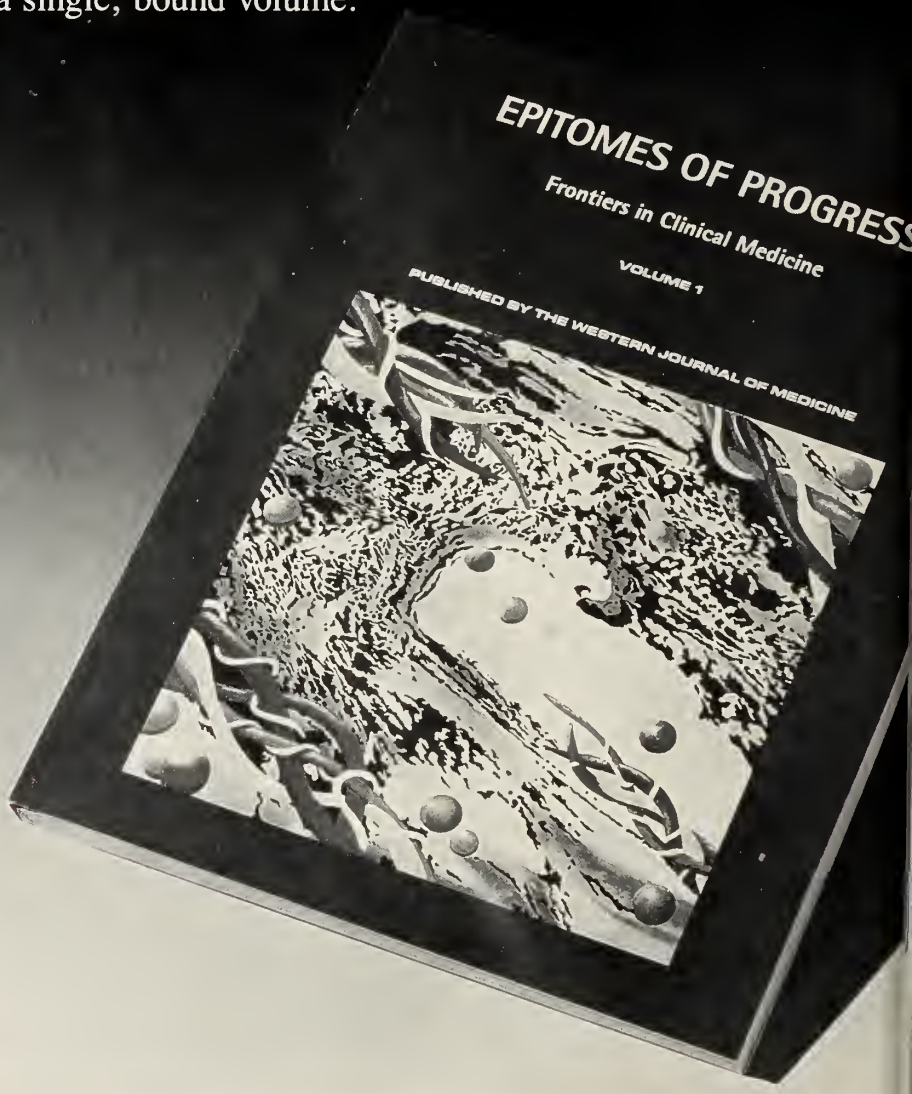

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Alaska State Medical Association—4107 Laurel St, Anchorage 99508. (907) 562-2662. Annual Meeting: July 8-10, 1992, Anchorage.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 4-6, 1992, Scottsdale.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 13-18, 1992, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1992, date and location to be announced.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1992, date and location to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 30-August 1, 1992, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1992, date and location to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 23-26, 1992, Sheraton Grand Torrey Pines, La Jolla, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 14-16, 1992, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1992, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. September 16-19, 1992, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 9-12, 1992, Jantzen Beach, Oregon.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 11-13, 1992, Jackson Lake Lodge, Moran.

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One Of A Kind

Zantac®

ranitidine HCl/Glaxo 150 mg and 300 mg tablets

Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B***: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

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Medi-Cal Approved

One Of A Kind

Please see Brief Summary of Prescribing Information on adjacent page.

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Treat hypertension at its source with...

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(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

CARDURA is well tolerated. Only three common side effects were different from placebo: dizziness, somnolence, and fatigue. These were generally mild and transient; only 2% of patients in placebo-controlled studies discontinued due to adverse effects—the same rate as placebo. Syncope has been reported, but rarely (< 1%).

Please see brief summary of prescribing information on adjacent page of this advertisement.

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ONCE-A-DAY

CARDURA®

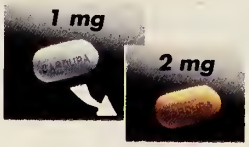
(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

Convenient once-a-day dosage

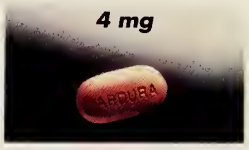
Most responsive patients are controlled with one daily dose of 4 to 8 mg[1]

—recommended initial dose is 1 mg, with dosage range of 1 mg to 16 mg per day.

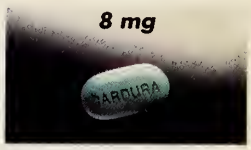
1 ***Begin all patients with CARDURA 1 mg once daily to minimize side effects. Evaluate supine and standing blood pressure. Prescribe CARDURA 2 mg once daily, if necessary.***



2 ***Evaluate for blood pressure control. Prescribe 4 mg once daily, if necessary.***



3 ***Evaluate for blood pressure control. Prescribe 8 mg once daily, if necessary. Maximum recommended dosage is 16 mg once daily.***



Reference: 1. Data available on request from Roerig.

CARDURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE
CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS
CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS
Syncope and "First-dose" Effect:
Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS
General:
1. Orthostatic Hypotension:
While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:
CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:
Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:
Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:
Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory test interactions:
None known

Cardiac Toxicity in Animals:
An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg, about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy
Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1: ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor, *Metabolic:* thirst, gout, hypokalemia, *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* hot flashes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE
The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION
DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.

HOW SUPPLIED
CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

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CAUTION: Federal law prohibits dispensing without prescription.

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cautions: Verapamil should be given cautiously to patients with impaired hepatic function evere dysfunction use about 30% of the normal dose) or impaired renal function, and patients ld be monitored for abnormal prolongation of the PR interval or other signs of overdosage. pamil may decrease neuromuscular transmission in patients with Duchenne's muscular rophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may ecessary to decrease verapamil dosage in patients with attenuated neuromuscular transmis- Combined therapy with beta-adrenergic blockers and verapamil may result in additive ative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have reports of excessive bradycardia and AV block, including complete heart block. The risks uch combined therapy may outweigh the benefits. The combination should be used only caution and close monitoring. Decreased metoprolol and propranolol clearance may occur n either drug is administered concomitantly with verapamil. A variable effect has been seen combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels 0% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of oxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully itored. Verapamil will usually have an additive effect in patients receiving blood-pressure-ering agents. Disopyramide should not be given within 48 hours before or 24 hours after pamil administration. Concomitant use of flecainide and verapamil may have additive effects nyocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine apy in patients with hypertrophic cardiomyopathy should be avoided, since significant otension may result. Concomitant use of lithium and verapamil may result in a lowering of m lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be itored carefully. Verapamil may increase carbamazepine concentrations during combined use. npin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. pamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and ase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium gonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may ntiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage ction may be required. There was no evidence of a carcinogenic potential of verapamil nistered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and pamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate well-controlled studies in pregnant women. This drug should be used during pregnancy, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing ld be discontinued during verapamil use.

erse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), ache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), ycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash 6), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The ving reactions, reported in 1.0% or less of patients, occurred under conditions where a al relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudi-n, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, ointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, ision, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, ness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, ting, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gyneco-ia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of YOCON® 1/12 gr. 5.4mg in bottles of 100's NDC 53159-001-01, 1000's NDC 53159-001-10 and Blister-Paks of 30's NDC 53159-001-30

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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ABSTRACTS FEBRUARY 1992

(Lucas LM, Colley CA: Recognizing and reporting adverse drug reactions. West J Med 1991 Feb; 156:172-175)

Although physicians in practice are most likely to see patients with adverse drug reactions, they may fail to recognize an adverse effect or to attribute it to a drug effect and, when recognized, they may fail to report serious reactions to the US Food and Drug Administration (FDA). To recognize and attribute an adverse event to a drug effect, physicians should review the patient's clinical course, looking at patient risk factors, the known adverse reactions to the suspected drug, and the likelihood of a causal relationship between the drug and the adverse event—based on the temporal relationship, response to stopping or restarting the drug, and whether other factors could explain the reaction. Once an adverse drug reaction has been identified, the patient should be informed and appropriate documentation made in the patient's medical record. Serious known reactions and all reactions to newly released drugs or those not previously known to occur (even if the certainty is low) should be reported to the FDA.

ADVERSE DRUG REACTIONS
DRUG REACTIONS
FOOD AND DRUG ADMINISTRATION

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ADVERSE DRUG REACTIONS
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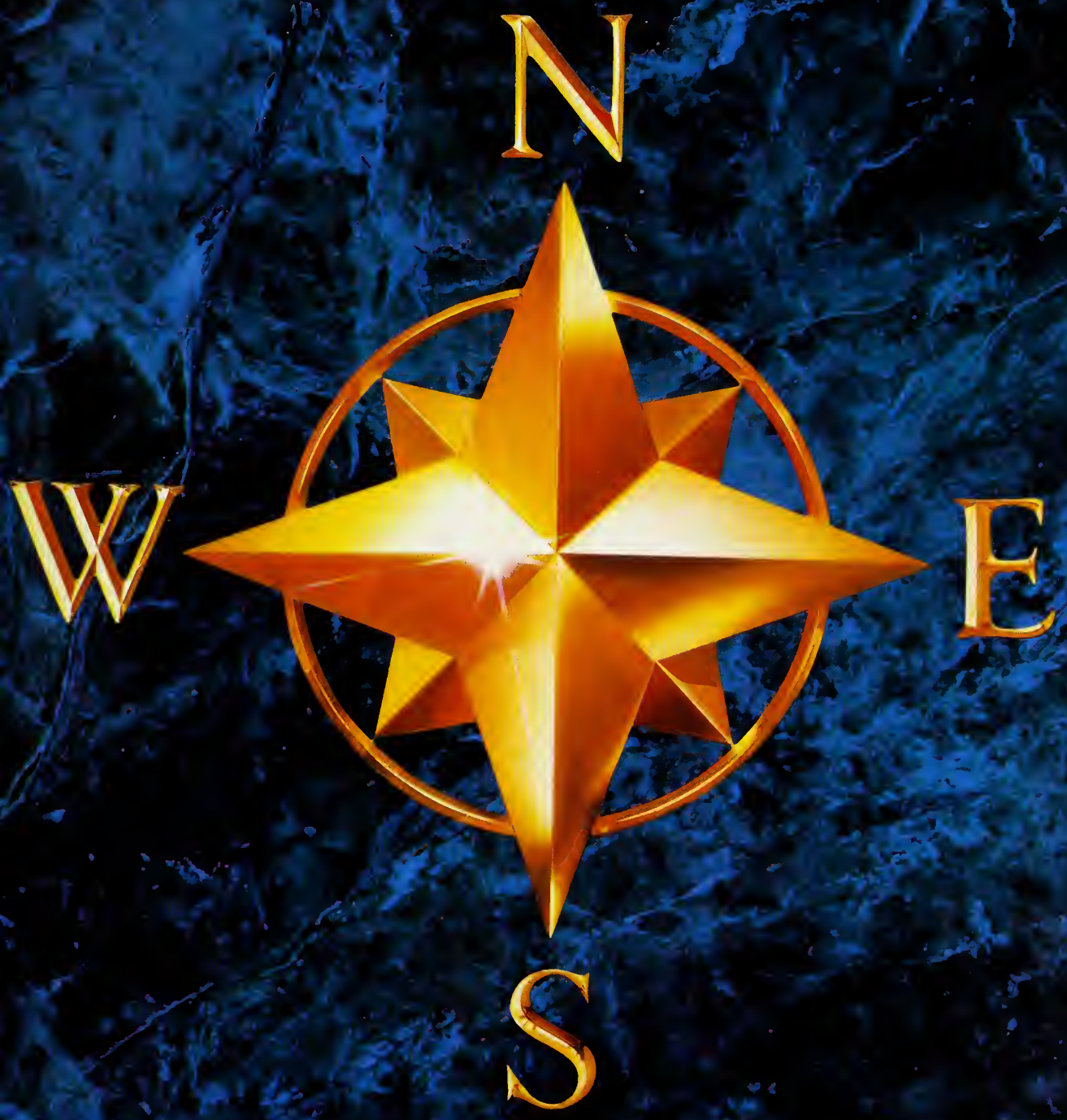
BRISTOL-MYERS SQUIBB INTRODUCES

A NEW DIRECTION IN LIPID MANAGEMENT



A NEW DIRECTION IN LIPID MANAGEMENT

PRAVACHOL™

pravastatin sodium 20 mg tablets

A distinct new option in cholesterol management for primary hypercholesterolemia when diet alone is inadequate

- Consistently and significantly reduces total C and LDL-C
- Positively affects other key lipids
- Excellent safety and tolerability profile
- True once-a-day dosing with or without food
- Prescribed for more than 1,000,000 patients worldwide[1]
- Studied in over 13,000 patients worldwide in clinical research[1]
- New hydrophilic structure; the clinical effect of hydrophilicity, if any, has not been established
- Administered in the active form

PRAVACHOL® is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

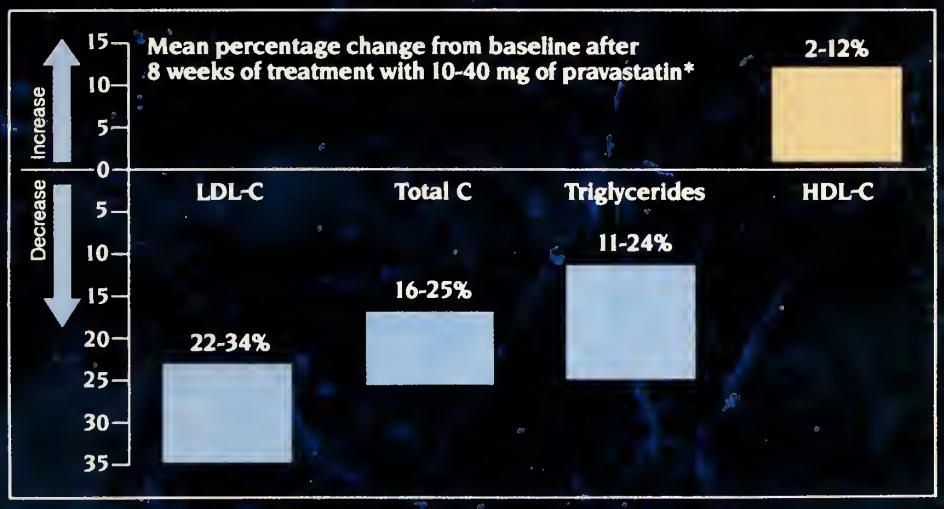
Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the final page of this advertisement.

A NEW DIRECTION IN LIPID MANAGEMENT

Effective cholesterol control

PRAVACHOL® is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Consistently and significantly reduces atherogenic LDL-C. Increases beneficial HDL-C.[2]



*Each bar represents a range of means derived from a single placebo-controlled study that included 55 patients treated with pravastatin.

Pharmacology and metabolism

- PRAVACHOL® is administered in the active form
- PRAVACHOL is hydrophilic; the clinical effect of hydrophilicity, if any, has not been established
- PRAVACHOL is selective to the primary site of cholesterol synthesis, the liver
- *In vitro* studies demonstrated that pravastatin is transported into hepatocytes with substantially less uptake into other cells

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the final page of this advertisement.

PRAVACHOL™

pravastatin sodium 20 mg tablets

A new direction in lipid management

A NEW DIRECTION IN LIPID MANAGEMENT

Safety profile promotes confidence

Possibly associated myopathy in only 1 patient in clinical trials (n>13,000)*[1]

Consider myopathy in any patient with diffuse muscle pain, tenderness, or weakness, particularly with malaise or fever. Advise patients to promptly report these symptoms. Discontinue pravastatin if myopathy is diagnosed or suspected.

In clinical studies, significant elevations of liver enzymes have been uncommon

- Increases in serum transaminase (greater than three times the upper limit of normal on two or more occasions) were seen in 1.3% of patients treated over an average of 18 months
- Elevations were generally reversible over time in patients discontinued from pravastatin; patients with biochemical findings were usually asymptomatic
- Active liver disease *or* unexplained transaminase elevations are contraindications to the use of pravastatin
- Liver function should be monitored before treatment and at recommended intervals–every 6 weeks for the first 3 months, every 8 weeks for the remainder of the first year, and periodically thereafter (e.g., at about 6-month intervals)

*A second patient developed myopathy when clofibrate was added to a previously well-tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the final page of this advertisement.

PRAVACHOL™

pravastatin sodium 20 mg tablets

A new direction in lipid management

A NEW DIRECTION IN LIPID MANAGEMENT

Well tolerated...

A side-effect profile generally comparable to placebo

Low incidence of side effects

Adverse clinical events attributed to study drug:	PRAVACHOL® (n=900)	Placebo (n=411)
Headache	1.7%*	0.2%
Cardiac chest pain	0.1	0.0
Rash	1.3	0.9
Nausea/vomiting	2.9	3.4
Diarrhea	2.0	1.9
Abdominal pain	2.0	3.9
Constipation	2.4	5.1
Flatulence	2.7	3.4
Heartburn	2.0	0.7
Fatigue	1.9	1.0
Chest pain	0.3	0.2
Localized pain	1.4	1.5
Myalgia	0.6	0.0
Dizziness	1.0	0.5
Urinary abnormality	0.7	1.2
Rhinitis	0.1	0.0
Cough	0.1	0.0

*Statistically different from placebo

Discontinuation rate from pravastatin (1.7%) was not statistically different from that of placebo (1.2%).

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PRAVACHOL™

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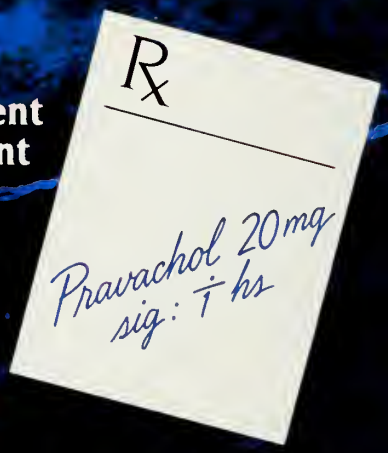
A new direction in lipid management

BRISTOL-MYERS SQUIBB INTRODUCES

A NEW DIRECTION IN LIPID MANAGEMENT

New PRAVACHOL™

pravastatin sodium 20 mg tablets



Provides an exceptionally convenient regimen in cholesterol management —once-a-day bedtime dosing

PRAVACHOL® offers true once-a-day dosing at bedtime, with or without food.

Usual dose: 20 mg at bedtime, with or without food

Dosage range:
10-40 mg. Available in 10 and 20 mg tablets.

Excellent monotherapy for a wide range of patients

PRAVACHOL is suitable for patients with primary hypercholesterolemia (Types IIa and IIb) with a cholesterol-lowering diet when diet alone has not been adequate.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the final page of this advertisement.

References: 1. Data on file, Bristol-Myers Squibb. 2. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

Bristol-Myers Squibb Company

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PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL), *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, betablockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥ 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p < 0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro,* with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae.* In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter^2). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: Skeletal Muscle and PRECAUTIONS: Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

(J4-422A)

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(Peterson MC, Holbrook JH, Hales D, Smith NL, Staker LV: Contributions of the history, physical examination, and laboratory investigation in making medical diagnoses. West J Med 1992 Feb; 156:163-165)

We report an attempt to quantitate the relative contributions of the history, physical examination, and laboratory investigation in making medical diagnoses. In this prospective study of 80 medical outpatients with new or previously undiagnosed conditions, internists were asked to list their differential diagnoses and to estimate their confidence in each diagnostic possibility after the history, after the physical examination, and after the laboratory investigation. In 61 patients (76%), the history led to the final diagnosis. The physical examination led to the diagnosis in 10 patients (12%), and the laboratory investigation led to the diagnosis in 9 patients (11%). The internists' confidence in the correct diagnosis increased from 7.1 on a scale of 1 to 10 after the history to 8.2 after the physical examination and 9.3 after the laboratory investigation. These data support the concept that most diagnoses are made from the medical history. The results of physical examination and the laboratory investigation led to fewer diagnoses, but they were instrumental in excluding certain diagnostic possibilities and in increasing the physicians' confidence in their diagnoses.

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HISTORY AND PHYSICAL EXAMINATION
LABORATORY INVESTIGATION

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2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

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Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency in patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

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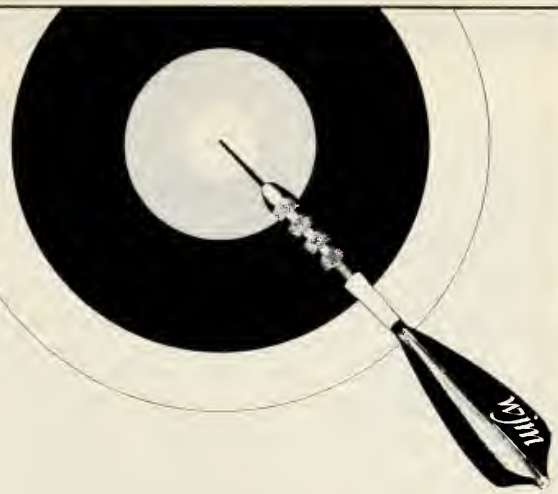

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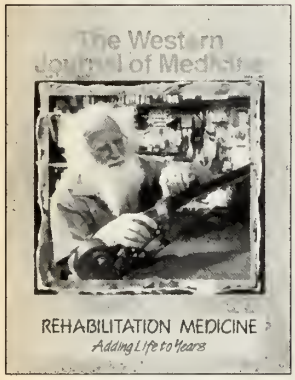

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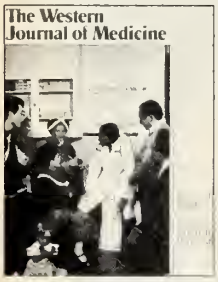

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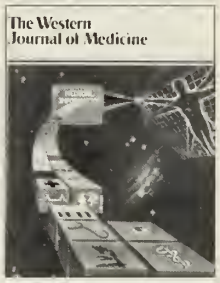

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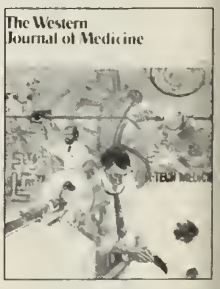

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Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 × 17.8 cm (5 × 7 in) glossy prints, with the figure number, author's name, and top of the photo indicated with a label on the back. Patients (and relatives) have a right to anonymity in published clinical documentation. Details that might identify patients should be avoided unless essential for scientific purposes. Masking of the eye region in photographs of patients may be inadequate protection of anonymity. If identification of patients is unavoidable, informed consent should be obtained, and this should be clearly stated in the article. Changing data on patients should not be used as a way of securing anonymity. Figure legends, to be typed in sequence on the same page, should be in complete sentences. Any figures or tables previously published must be accompanied by a letter of permission to borrow from the copyright holder (the previous publisher). The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

All manuscripts will be subject to peer review to determine the originality, validity, and importance of con-

tent and conclusions. Reviewers' comments will be returned with rejected manuscripts at the discretion of the Editors. All reviewers will remain anonymous. Any conflict of interest, actual or potential, will have been revealed to the Editors.

All accepted manuscripts are subject to copy editing, and the corresponding author is sent edited galley proofs for approval and necessary minor changes. Excessive changes at this stage may result in a delay of publication or withdrawal of the paper. No changes will be made after the final, edited version has been approved by the corresponding author without notifying the author. It is the corresponding author's responsibility to clear all corrections and changes with his or her coauthors.

Reprints

A form to order reprints will be sent to the author when the article is published.

References

All references should be cited in the text and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in *WJM* style per the examples given below.

(All references should be medical, scientific, or scholarly publications. Others—newspapers, magazines, etc—should be kept to a minimum and included in the text.)

Journal Articles

Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year).

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

CHECKLIST

- Original manuscript and 2 copies
- **Everything** double-spaced
- Illustrations, black and white glossy, identified with lead author's name—3 sets, plus figure legends that describe fully and in complete sentences what the figure depicts
- Letter of transmittal that includes release of copyright, statement of conflict of interest, and authorship responsibility, **signed by all authors**
- A 200-word abstract
- Title page that includes current affiliation of all authors and address **and telephone number** for corresponding author
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- All references numbered consecutively, double-spaced, and cited in text. No unpublished data or nonscientific publications listed in references (include in text)

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CMA's Department of Physician Education has produced a new CME program, "HIV Risk Assessment: Methods and Guidelines," which is available free to physicians. This program teaches effective strategies developed by expert physicians to identify patients who are potentially at risk for HIV infection. Worth one hour of CME Category I credit, the program is designed for groups of 5-20 physicians.

The program features CMA's award-winning, 11-minute video, "Let's Talk," which highlights several methods physicians can use to perform HIV assessment with patients. Participants receive a course outline, camera-ready slide reproductions, a compilation of state laws pertaining to HIV/AIDS, community resource guide to HIV testing and counseling, risk assessment guidelines, and a model HIV consent form and patient information pamphlet.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

February 14-16—**Anesthesia for the '90s: 18th Annual Scientific Meeting.** University of Arizona College of Medicine at Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: Beverly Richter, (602) 246-8901.

February 20-22—**18th Annual Frontiers in Ophthalmology.** St Luke's Medical Center at Red Lion's LaPosado Resort, Scottsdale. Thurs-Sat. Contact: Christine Campbell, (602) 820-7027.

February 24-27—**Practical Radiology.** University of Arizona College of Medicine at Loews Ventana Canyon Resort, Tucson. Mon-Thurs. Contact: U of A.

February 25-28—**14th Annual Tucson Hospitals Medical Education Medical Conference—Clinical Update.** Cascade Village, Durango, CO. Tues-Fri. Contact: Richard Dale, MD, (602) 885-2303.

February 27-28—**Advances in Obstetrics and Gynecology.** Maricopa Medical Center and Phoenix OB/GYN Society at Scottsdale Hilton, Scottsdale. Wed-Fri. Contact: Marilyn Harter, (602) 266-6321.

February 27-29—**Geriatric Medicine Update and Board Certification Review Course.** University of Arizona College of Medicine at Doubletree Hotel, Tucson. Thurs-Sat. Contact: U of A.

February 27-March 1—**Teaching Each Other—Arizona Academy of Family Physicians 43rd Annual Scientific Assembly.** Wyndham Paradise Valley Resort, Scottsdale. Thurs-Sun. Contact: Jerry Davis, (602) 249-2021.

March 5-7—**Practical Management of Rheumatic Disease.** University of Arizona College of Medicine at Doubletree Hotel, Tucson. Thurs-Sat. Contact: U of A.

March 8-11—**Fiberoptics Workshops for the Difficult Airway.** University of Michigan College of Medicine at Red Lion's La Posada Resort, Scottsdale. Sun-Wed. Contact: Tami Gibson, (800) 962-3555.

March 11-14—**Symposium on Low Back Pain: The Present and the Future.** University of Arizona College of Medicine at the Sheraton El Conquistador Golf and Tennis Resort, Tucson. Wed-Sat. Contact: U of A.

March 12-14—**Nineteenth Annual Symposium—Recent Advances in Neurology and Neurosurgery.** St. Joseph's Hospital and Medical Center, Barrow's Neurological Institute at Camelback Inn, Scottsdale. Thurs-Sat. Contact: Toby Anchie, (602) 285-3579, or (800) BARROW-1.

March 14-19—**First Annual Samaritan Winter Medical Symposium.** Good Samaritan Regional Medical Center at Park City, Utah. Sat-Thurs. Contact: Roxanne Carstensen, 495-4929, or (800) 443-5972.

March 19-20—**Clinical Reviews 1992.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Thurs-Fri. Contact: Mayo Clinic-Scottsdale.

March 21—**Primary Management of Common Cardiovascular Diseases.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Sat. Contact: Mayo Clinic-Scottsdale.

March 21—**ENT for the Primary Care Physician.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Sat. Contact: Mayo Clinic-Scottsdale.

March 23-25—**Perspectives in Hepatobiliary and Pancreatic Surgery.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Fri-Sun. Contact: Mayo Clinic-Scottsdale.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724 (602) 626-7832.

March 27-28—**Pediatric Imaging Update.** University of California, San Francisco, School of Medicine at Camelback Inn, Scottsdale. Fri-Sat. Contact: (415) 476-5731.

March 28-30—**Electromyography in Clinical Practice.** Mayo Clinic-Scottsdale at Ashton B. Taylor Auditorium, Mayo Clinic-Scottsdale. Sat-Mon. Contact: Mayo Clinic-Scottsdale.

March 30-April 3—**Radiology Spring Training.** University of California, San Francisco, School of Medicine at Camelback Inn, Scottsdale. Mon-Fri. Contact: (415) 476-5731.

June 4-6—**Arizona Medical Association—Annual Meeting.** Scottsdale. Thurs-Sat. Contact: ArMA.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For more information on accreditation or certification, please write to the above address.

ALLERGY

March 27-28—**Asthma and Allergy in the 1990s.** Medical Education Resources at Wyndham Hotel, Palm Springs. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

ANESTHESIOLOGY

March 13-17—**66th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at San Francisco Hilton & Towers. Fri-Tues. Contact: Anne Maggiore, IARS, 2 Summit Park Dr, Ste 140, Cleveland, OH 44131. (216) 642-1124.

March 21-22—**Postgraduate Assembly.** Los Angeles County Society of Anesthesiologists at Sheraton Universal Hotel, Universal City. Sat-Sun. $200. Contact: Michael Carlson, 1903 Redondo Ave, Long Beach 90804. (213) 597-2661.

March 21-26—**20th Obstetric Anesthesia Conference.** Ohio State University Hospitals at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

May 17-22—**Anesthesiology Review Course.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

CARDIOLOGY

March 20-21—**Cardiac Diagnostic Methods & Risk Management.** Medical Education Resources at Caesars Palace, Las Vegas, Nevada. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

April 4—**Practical Cardiology for the '90s.** Grossmont Hospital at La Mesa. Sat. Contact: Karen Hamilton, PO Box 158, La Mesa 91944-0158. (619) 589-4168.

April 6-11—**31st Annual Cardiology Retreat.** Scripps Clinic and Research Foundation at Rancho Santa Fe. Mon-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 21-23—**2nd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

(Continued on Page 144)

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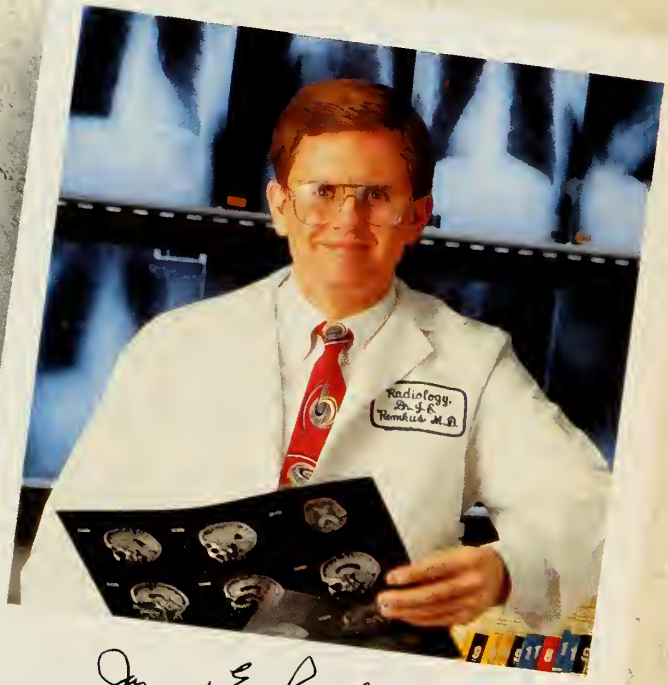

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(Continued from Page 142)

May 1-2—**2nd International Symposium on Thrombolytic Therapy in Acute Ischemic Stroke.** Scripps Clinic and Research Foundation at San Diego Marriott, La Jolla. Fri-Sat. Contact: Scripps Clinic, Box 403C, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 26-28—**2nd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

DERMATOLOGY

February 27—**Problems of the Aging Skin.** Stanford Medical Center at Palm Springs. Thurs-Sun. Contact: Pamela Bain, R-144, Stanford 94305. (415) 723-7854.

July 14-18—**Dr. Hugh Greenway's Eighth Annual Conference: Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation at UCSD Campus and Scripps Clinic, La Jolla. Wed-Sat. 36 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

July 30-August 1—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 24 hrs. $425. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

EMERGENCY MEDICINE

February 23-28—**Emergency Medicine.** UCD at Incline Village, Nevada. Sun-Fri. Contact: UCD.

February 23-28—**Squaw Valley Annual Winter Emergency Medicine Conference.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Sun-Fri. 20 hrs. $395. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 888-5632.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

March 8-13—**13th Annual Mammoth Mountain Emergency Medicine Ski Conference.** CAL/ACEP and Orange County Emergency Department at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Mark Song, Medical Conferences, PO Box 52-B, Newport Beach 92662. (714) 552-0831.

March 16-20—**Emergency Medicine Symposia II.** UCSD at Basic Science Building. Mon-Fri. Contact: UCSD.

March 20-21—**Advances in Emergency Medicine: Toxicology and Infectious Diseases.** UCLA at Hotel del Coronado. Fri-Sat. 13.5 hrs. $125. Contact: UCLA Extension.

April 1-4—**8th Annual Advances in Emergency Medicine.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Sat. $455. Contact: UCSF.

May 6-10—**14th Biannual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 18 hrs. $200-$435. Contact: UCSD.

May 11-15—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. Contact: UCSD.

June 22-26—**Emergency Medicine Symposia III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. Contact: UCSD.

ENDOCRINOLOGY AND METABOLISM

March 4-5—**Advances in Endocrinology and Metabolism.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Thurs. 14.5 hrs. $295. Contact: UCSF.

March 6—**18th Annual Diabetes Symposium.** UCD at Sacramento. Fri. 6 hrs. $140. Contact: UCD.

March 6-7—**Diabetes Update.** UCSF at Pan Pacific Hotel, San Francisco. Fri-Sat. 10 hrs. $245. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

February 17-19—**Issues in Men's Health.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 21-22—**Cardiovascular and Pulmonary Diseases: Noninvasive Diagnostic Methods for Primary Care Physicians.** Medical Education Resources at Caesar's Palace, Las Vegas, Nevada. Fri-Sat. 12 hrs. Contact: Laurie Christopher, (303) 465-6402.

February 29—**Dermatology for the Primary Care Physician.** UCLA at Biltmore Hotel, Los Angeles. Sat. 5.5 hrs. $55. Contact: UCLA Extension.

March 25-27—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF. Wed-Fri. 15.5 hrs. Contact: UCSF.

March 27-28—**Peripheral Vascular Disease: Noninvasive Diagnosis for Primary Care Physicians.** Medical Education Resources at Doubletree Resort at Desert Princess Country Club, Palm Springs. Fri-Sat. 12 hrs. Contact: Laurie Christopher, (303) 465-6402.

April 3-4—**Peripheral Vascular Disease: Noninvasive Diagnosis for Primary Care Physicians.** Medical Education Resources at Caesar's Palace, Las Vegas, Nevada. Fri-Sat. Contact: Laurie Christopher, (303) 465-6402.

April 4—**Cardiology for Primary Care.** UCDMC at Cancer Center Auditorium. Sat. Contact: UCD.

April 4-11—**5th Annual Primary Care Medicine: Update 1992.** UCSF at Maui Intercontinental, Wailea, Maui, Hawaii. 1 week. $540. Contact: UCSF.

April 9-11—**Advances in Rheumatology for Primary Care Physicians.** UCSF at Le Meridien Hotel, San Francisco. Thurs-Sat. $240. Contact: UCSF.

April 10-12—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Vacation Village, San Diego. Fri. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

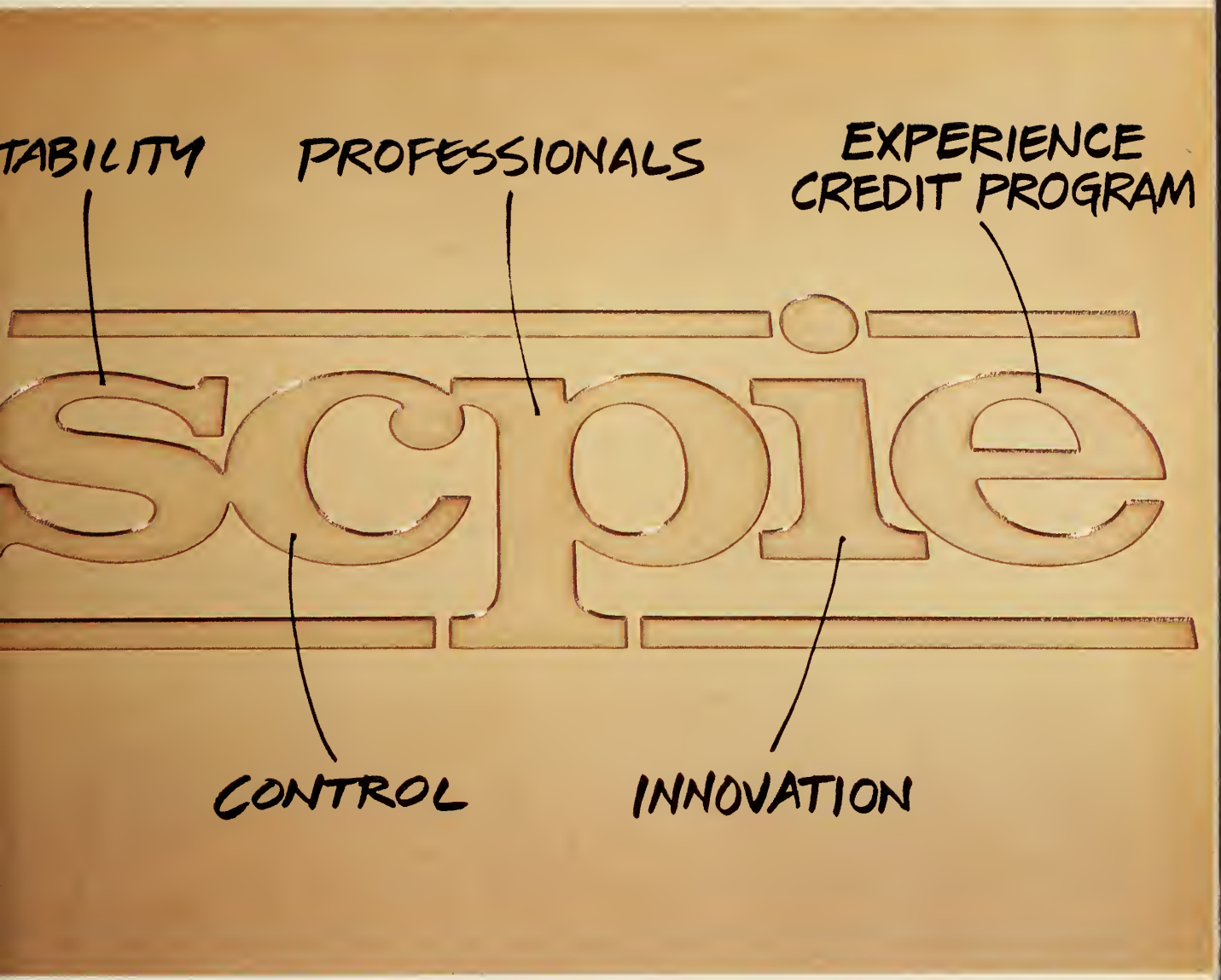
June 15-20—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Marriott Hotel, Newport Beach. Mon-Sat. Contact: UCI.

July 6-9—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

GASTROENTEROLOGY

February 29-March 1—**Endoscopy Update 1992.** Southern California Society for Gastroenterology at Century Plaza Hotel, Los Angeles. Sat-Sun. Contact: Joyce Fried, University of California Brain Research Institute, Los Angeles 90024.

(Continued on Page 146)



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CONTINUING MEDICAL EDUCATION

(Continued from Page 144)

GERIATRICS

March 6-8—**Recent Advances in Geriatric Medicine-Healthy People 2000: A New Look at Screening, Prevention and Rehabilitation in the Elderly.** UCSD at Pan Pacific Hotel, San Diego. Fri-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 16-17—**Exercise in Geriatric Care.** VA Sepulveda Medical Center at Burbank. Mon-Tues. Contact: Symposium Secretary, VA Medical Center, GRECC (11E), 16111 Plummer St, Sepulveda 91343. (818) 895-9311.

INFECTIOUS DISEASES

April 25—**HIV Update.** UCDMC at Cancer Center Auditorium. Sat. Contact: UCD.

April 29-May 1—**13th Annual Advances in Infectious Diseases.** UCSF at San Francisco. Wed-Fri. $400. Contact: UCSF.

May 6-8—**13th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. $400. Contact: UCSF.

INTERNAL MEDICINE

February 22-27—**Topics and Advances in Internal Medicine.** UCSD at Sheraton Harbor Island, San Diego. Sat-Sun. Contact: UCSD.

February 23-25—**5th Annual Congress of the North American Society of Phlebology on the Advances in Sclerotherapy and the Advances in Surgical and Medical Treatment of Venous Disease.** North American Society of Phlebology and the American Academy of Dermatology at Grand Hyatt Union Square, San Francisco. Sun-Tues. 14 hrs. Contact: NASP, 204 N El Camino Real, E-234, Encinitas 92024. (619) 942-8380.

February 23-28—**Emergencies in Internal Medicine: 1992. 15th Annual UCD Winter Conference.** UCD at Hyatt Regency, Lake Tahoe. Sun-Fri. 25 hrs. $465. Contact: UCD.

February 27-29—**1992 Zimmerman Conference: Progress in Vascular Biology, Hemostasis and Thrombosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 20-26—**Internal Medicine 1992: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado. Fri-Thurs. 54 hours. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

May 11-15—**20th Annual Advances in Internal Medicine.** UCSF at Ritz-Carlton Hotel, San Francisco. Mon-Fri. 33 hrs. $610. Contact: UCSF.

June 22-26—**20th Annual Advances in Internal Medicine.** UCSF at Cole Hall Parnassus Campus. Mon-Fri. 32 hrs. $610. Contact: UCSF.

NEUROLOGY

July 30-August 1—**New Advances in Common Neurological Disorders.** UCSD at Catamaran Hotel, San Diego. Thurs-Sat. Contact: UCSD.

OB/GYN

April 2-4—**Gynecologic Surgery.** Memorial/UCI Center for Health Education at Marquis Hotel, Palm Springs. Thurs-Sat. Contact: UCI.

April 2-4—**Ultrasound Update.** Memorial/UCI Center for Health Education at Bally's Hotel, Las Vegas. Thurs-Sat. Contact: UCI.

April 8-12—**Pacific Coast Fertility Society: Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Director of Medical Education, 12760 La Mirada Blvd, Ste 220, La Mirada 90638. (213) 947-7068.

June 5-7—**Advanced Fetal Heart Rate Monitoring.** Memorial/UCI Center for Health Education at Radisson Hotel, Palm Springs. Fri-Sun. Contact: UCI.

July 29—**10th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Wed-Sat. Contact: UCI.

OCCUPATIONAL/ENVIRONMENTAL

April 3-4—**Management of Occupational Health Problems in Primary Care Settings.** University of California Berkeley at Sunnydale Hilton Hotel. Fri-Sat. 11 hrs. $275. Contact: Mary Hughes, (510) 642-5507.

June 5-6—**Occupational and Environmental Medicine.** UCD. Fri-Sat. Contact: UCD.

July 26-31—**Sports Medicine.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

ONCOLOGY

February 29—**Neo Adjuvant Approach to Non-Small Cell Lung Cancer.** UCD at Incline Village, Nevada. Sat. Contact: UCD.

February 29-March 1—**Advances in Local and Systemic Therapy in Non-Small Cell Lung Cancer.** UCD at Hyatt Regency, Lake Tahoe, Incline Village, Nevada. Sat-Sun. 9 hrs. $150. Contact: UCD.

March 5-7—**7th International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at San Diego Marriott. Thurs-Sat. Contact: UCSD.

March 20-21—**Non-palpable Breast Cancer: Diagnosis and Management.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. 8 hrs. $140. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 30-May 3—**Breast Cancer Conference.** Memorial/UCI Center for Health Education at Hyatt Regency, Long Beach. Thurs-Sun. Contact: UCI.

OPHTHALMOLOGY

March 6-7—**6th Annual Visions in Ophthalmology: '92.** Scripps Memorial Hospital at Mericos Eye Institute. Fri-Sat. Contact: Meeting Management, (619) 453-6222.

March 12-13—**Ophthalmology in Developing Countries: An International Symposium.** UCSF at Holiday Inn, San Francisco. Thurs-Fri. 15 hrs. $350. Contact: UCSF.

May 15-16—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 403C, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

ORTHOPEDICS

March 15-20—**The Spine: Current Concepts of Diagnosis and Treatment.** Vanderbilt University Medical Center Department of Orthopaedics at Grand Hyatt Wailea, Maui, Hawaii. Sun-Fri. $575. Contact: The Spine/Current Concepts, c/o Unconventional Inc, 3960 Park Blvd, Ste E, San Diego 92103. (619) 692-9115.

June 14-19—**16th Annual Fingers to the Toes.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. Contact: UCD.

PAIN MANAGEMENT

February 19-22—**The Practicing Physician's Approach to the Difficult Headache Patient.** University of Chicago School of Medicine at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 878-0396.

PATHOLOGY

February-May 1992—**Bay Area Seminars in Cytopathology: 1992.** UCSF at Health Sciences West on Campus. Thursdays. 10 hrs. $150. Contact: UCSF.

February 24-26—**Fine Needle Aspiration Basic Tutorial.** UCSF at Squaw Valley. Mon-Wed. 12 hrs. $850. Contact: UCSF.

February 27-29—**Fine Needle Aspiration Advanced Tutorial.** UCSF at Squaw Valley. Thurs-Sat. 12 hrs. $850. Contact: UCSF.

April 11—**7th Annual Conference: New Treatment in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 16—**Fine Needle Aspiration Basic Tutorial.** UCSF. Sat. 12 hrs. $650. Contact: UCSF.

May 21-22—**Curent Issues in Anatomic Pathology: 1992.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Fri. 13 hrs. $325. Contact: UCSF.

PEDIATRICS

March 4-6—**17th Annual Care of the Sick Newborn.** Memorial/UCI Center for Health Education at Long Beach. Wed-Fri. Contact: UCI.

March 13-15—**Pediatrics in Yosemite.** Valley Children's Hospital. Fri-Sun. 12 hrs. $370-$425. Contact: Valley Children's Hospital, Marketing & Planning, 3151 N Millbrook, Fresno 93703. (209) 225-3000.

(Continued on Page 154)

Come to San Diego for...

Advances In Internal Medicine: 1992

American College of Physicians
73rd Annual Session
March 26-29, 1992

Pre-Session Courses
March 24-25, 1992

Broaden your understanding and refresh your knowledge of internal medicine and its related subspecialties in over 300 scientific sessions. PLUS, explore this year's curriculum on Men's and Women's Health Issues, covering such topics as:

- Breast Cancer
- Hormone Replacement during Menopause
- Prostatic Cancer
- Sexually Transmitted Diseases...and more.

Pre-Registration Deadline:
February 24, 1992

For information on registering, call our Registration Hotline: 800-523-1546, ext. 2429 or dial direct 215-351-2429.

How to Register

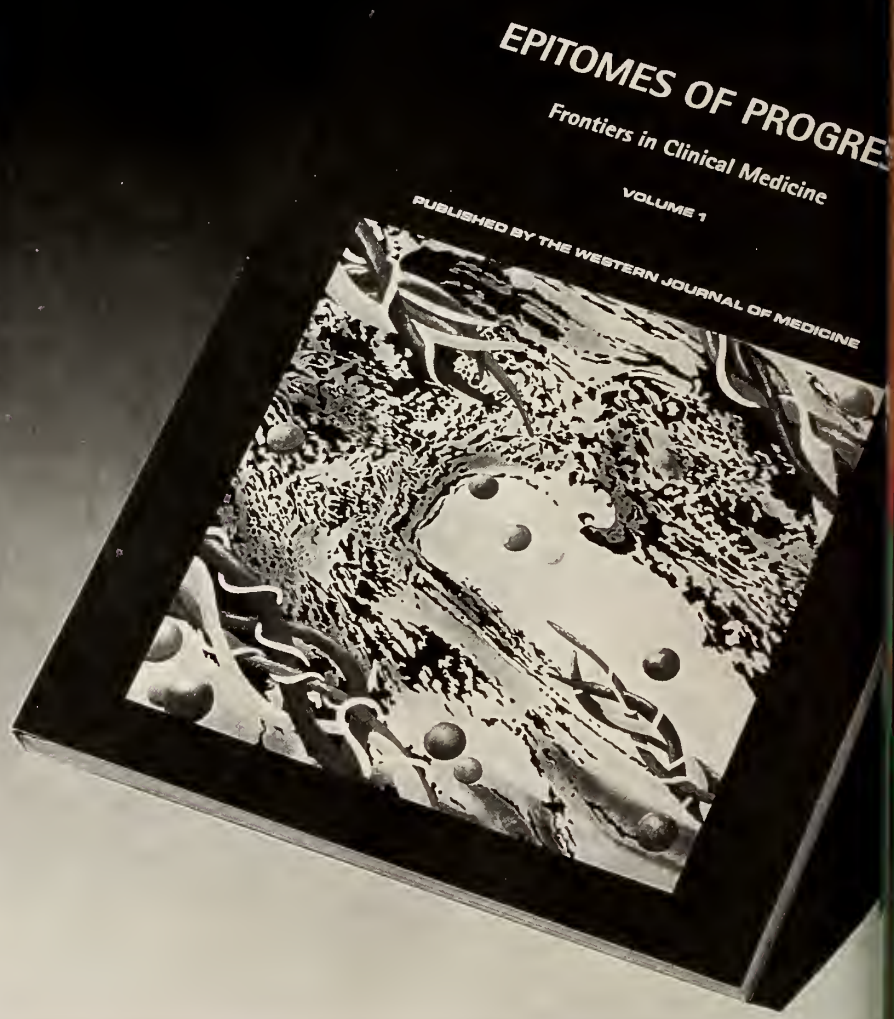
ACP Membership: Consult your Advance Program mailed in December. It contains information about the meeting and how to register.

Nonmembers: Watch for the complete schedule of events and a registration form in the Annual Session Digest appearing in the December 15, 1991, and January 1 and February 1, 1992, issues of *Annals of Internal Medicine.*

A|C|P

epitome

i-'pit-ə-mē\ *n* [L, fr. Gk *epitomē*, fr. *epitemnein* to cut short, fr. *epi-* + *temnein* to cut — more at TOME] (1520) **1 a** : a summary of a written work **b** : a brief presentation or statement of something **2** : a typical or ideal example: EMBODIMENT (the British monarchy itself is the ~ of tradition — Richard Joseph) **3** : Plural — *Epit-o-mes* — A regular FEATURE of *The Western Journal of Medicine*, now available in a single, bound volume.



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Annual Session and Western Scientific Assembly

March 13-18, 1992
Disneyland Hotel
Anaheim, CA

California Medical Association

CMA's '92 Annual Session and

GOLDEN APPLE AWARD AND RECEPTION

"Student Stages"

Friday, March 13, 5:30 pm
Disneyland Hotel

Doctor Faith Thayer Fitzgerald has been selected by the Committee on Scientific Assemblies to receive CMA's 1992 Golden Apple Award. This award spotlights exceptional physicians who have made a lifelong commitment to teaching and are renowned for their charismatic, scientific and educational talents.

Doctor Fitzgerald decided to become an internist and teacher in the spring of 1967, during her third year medicine clerkship at UC, San Fran-cisco. She joined the faculty of UC, Davis in 1980, becoming Professor of Medicine in 1986. In addition to her teaching role at UC Davis, Doctor Fitzgerald has served as Dean of Students and, more recently, as Program Director in Internal Medicine and Vice Chair of the Department of Medicine.

Beyond the outstanding contributions she has made at UC, Davis, Doctor Fitzgerald has also been a visiting professor at universities across the United States, and her excellence in the field of education has brought her numerous awards. In 1991 Doctor Fitzgerald received the most prestigious honor of being elected Master by the Board of Regents of the American College of Physicians. It is a position held by a select group of 223 physicians, among which only 11 are women.

We encourage all to attend CMA's Golden Apple Award presentation and reception at which time Doctor Fitzgerald will speak on "Student Stages."

The financial assistance of Cooperative of American Physicians, Inc. - Mutual Protection Trust is gratefully acknowledged in making this reception possible.

Friday, March 13

01 Basic Cardiac Life Support

02 Newer Aspects of Chronic Viral Hepatitis

03 Special Procedures in Office Gynecology

04 Working With the Handicapped and Disabled: The Physician's Role

05 Newer Concepts in the Treatment of Pulmonary Infections

06 1992 Update on Osteoporosis

07 Update on the Pharmaceutical Management of Anxiety Associated with Medical Illness, Drug Abuse and Other Conditions

08 Surviving Malpractice Litigation

Saturday, March 14

09 Advanced Cardiac Life Support - Provider Course

10 Cosmetic Improvement of Sun-Damaged Skin

11 Coronary Artery Disease: It's Killing Us

12 Management of Headache and Other Pains in the Neck

13 Practical Eye Care for the Primary Physician

14 Management of Common ENT Emergencies

15 Imaging In The 1990's: A Guide To The Selection Of Cost Effective Diagnostic Imaging Pathways

16 Futile Medical Treatment and the Limits of Patient Autonomy

17 Breast Cancer: Detection and Treatment

18 Update on Ischemic Cerebrovascular Disease

19 What's New in Evaluation and Treatment of Low Back Pain

20 Pediatric Infectious Diseases 1992: What's Hot, What's Not

Western Scientific Assembly

Sunday, March 15

21 Advanced Cardiac Life Support - Retraining Course

22 Urology for the Primary Care Physician - 1992

23 All You Want to Know About the Match: A Workshop on Residency Selection and Career Planning

24 Skin Cancer Recognition and Its Management

25 Update on Neurology for the Practicing Physician: Causes and Effects of Altered Mental Status

26 Exercise, Fitness, and Health: The Physician's Role

27 Suture Course

28 Mind If I Breathe? The Effects of Secondhand Smoke

29 Target Intervention: How To Help Your Patients Stop Smoking

30 A Critical Look at the Washington Scene

31 Avoiding Liability in the era of HIV/AIDS - What Every Physician Must Know

Monday, March 16

32 Twenty Ways I've Changed My Practice in Emergency Medicine

33 Patients Who Try Our Patience

34 Controversies in Pharmacotherapy of Asthma

35 Too Young To Die: Clinical Opportunities to Prevent Injury

36 Planning for Retirement and a Stable Financial Future

To receive a copy of the 40-page Advance Program Guide, which provides details on all programs above, please call (415) 882-3384.

DISTINGUISHED SPEAKER

Sunday, March 15, 1992, 1:00 pm

Third-Generation Managed Care:

Will Future Organized Care Systems Be More Physician Friendly?

Doctor Jacque J. Sokolov is vice president and medical director of the Southern California Edison Company (SCE) which provides one of the largest self-administered, self-funded health care plans in America, covering 55,000 people and expending over $100 million annually. He is responsible for health care benefits and plan administration; provider services; managed care services; health care systems and budgets; preventive health education and communications; as well as clinic and pharmaceutical services.

Doctor Sokolov received a B.A. in medicine, magna cum laude, from the University of Southern California and an MD with honors from the USC School of Medicine. He is currently a clinical professor of medicine at the USC School of Medicine and a visiting lecturer at UCLA and the Massachusetts Institute of Technology. Before joining SCE, Doctor Sokolov served as a health care consultant to a number of Fortune 100 firms.

We invite all to come listen to Doctor Sokolov's provocative discussion on the development of third- generation managed care programs.

EXHIBITS

During the Western Scientific Assembly, the Exhibit Hall will feature exhibits for everyone: pharmaceuticals, educational displays, computer systems, office systems, insurance, investment opportunities, medical testing systems, health and home products, and much more.

1992 Annual Session and Western Scientific Assembly

CONCURRENT EVENTS

CMA HOUSE OF DELEGATES

The CMA House of Delegates meets each day, Saturday through Wednesday. House Speaker, Doctor Jack McCleary, notes that the current schedule of the House provides delegates with time to attend scientific programs, view the exhibits and participate in delegation caucuses.

Highlights of this year's House will be the farewell address of outgoing CMA President, Howard L. Lang, MD, a Greenbrae obstetrician-gynecologist, and the inaugural address of CMA's President-Elect, Richard F. Corlin, MD, A Santa Monica Gastroenterologist.

YOUNG PHYSICIANS SECTION ANNUAL ASSEMBLY

The CMA established the Young Physicians Section (YPS) in March 1989 to represent physicians who are CMA members under the age of 40 or in the first five years of practice. During the Assembly, representatives will elect officers for the Section and discuss issues of interest and concern to young physicians. The Assembly will also feature Assemblyman Bruce Bronzan (D-Fresno). Registration will begin at 8:30 am on Friday, March 13 at the Disneyland Hotel, and the Assembly will convene from 9:30 am to 5:30 pm. All California young physicians are invited to attend this free meeting. For additional information, please contact Anna Hanson at (916) 736-1188.

SPECIAL EVENTS 1992

When you're done attending meetings or visiting the exhibits, take advantage of the great special events CMA has available. Registrations can be made at the Special Events Booth in the Disneyland Hotel.

- Fun Day at Disneyland
- Universal Studios/Hollywood
- Whale Watching and Sunday Brunch
- Early California Tour
- Laguna Arts and Antiques
- Newport Beach Dine-A-Round

GENERAL INFORMATION

LOCATION

The CMA 1992 Western Scientific Assembly will be held at the Disneyland Hotel, 1150 West Cerritos Avenue, Anaheim, CA 92802. Call (714) 778-6600 for hotel registration information.

FEES

There is no general registration fee for CMA members, Auxiliary members, fellows, residents, interns and medical students, nor to their guests who do not attend educational programs.

Nonmember physicians are required to pay a general registration fee of $120 per day or $300 for the entire event; nurses and allied health professionals are required to pay a $50 fee.

ADVANCE REGISTRATION CLOSES FEBRUARY 14, 1992

Attendees may register on site at the Disneyland Hotel's Center Lounge:

Thursday, March 12, 1:00 pm to 7:00 pm
Friday, March 13, 7:00 am to 5:00 pm
Saturday, March 14, 7:00 am to 5:00 pm
Sunday, March 15, 7:00 am to 5:00 pm
Monday, March 16, 7:30 am to 3:00 pm

On Tuesday, March 17, the registration desk will move to the House of Delegates Registration Area outside the Marina Ballroom from 9:00 am to 12:00 noon.

FOR MORE INFORMATION

Contact CMA, Western Scientific Assembly (415) 882-3384

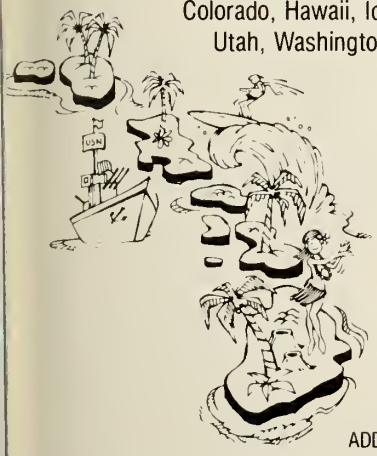
The Western Journal of Medicine

Medical Student 1992 Writing Award Competition

$1,000 CASH PRIZE!

■ Enter your original medical research or medical review article—the article must be of interest to clinicians and not previously published. The winner will receive a $1,000 cash prize and a two-year subscription to **The Western Journal of Medicine.** The winning article will be published in **WJM. Deadline to enter, March 1, 1992.**

■ **WJM** is the official journal of ten western medical associations and six clinical investigation/specialty societies. This competition is only open to medical students attending school in Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, or Wyoming.



■ **WJM** is clinically oriented, national in scope, and not confined to any single specialty. Your article must be written in **WJM** style and be of interest to our readers. If, in the judgment of the editorial board, no articles meet the standards of **WJM,** no award will be made.

ADDITIONAL RULES:

Articles must be 3,000 to 4,000 words in length. The manuscript must be identified as submitted for nsideration for this award.

Co-authorship is permitted if all authors meet the qualifications. The $1,000 award will be divided equally ong the co-authors.

Articles must conform to **WJM's** style—our style guide, "Instructions for Authors," appears in the January July issues, or you may write our editorial department for a copy of the guide.

Articles will be judged by the editors and the editorial and advisory boards of the journal.

The winner will be announced and the article published in **WJM.** In case of a tie, the $1,000 award will be ded equally.

DEADLINE: MARCH 1, 1992.

For additional information write to:

THE WESTERN JOURNAL OF MEDICINE
Editorial Office/Award Competition
P.O. Box 7602
San Francisco, CA 94120-7602

(Continued from Page 146)

April 24-26—**1992 West Coast Regional Conference on Pediatric Psychology.** UCSF at Union Square Holiday Inn, San Francisco. Wed-Fri. Contact: UCSF.

May 14-16—**25th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $325. Contact: UCSF.

June 26-28—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Wed-Fri. Contact: Continuing Education, (619) 576-4072.

PSYCHIATRY

February 15-16—**Victims of Abuse: The Emotional Impact of Child and Adult Trauma.** San Diego Psychoanalytic Society and Institute at Hyatt Regency La Jolla at Aventine. Sat-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 29-March 1—**Basic Hypnosis: A Hands-On Workshop and Special Advanced Workshop.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sat-Sun. 13 hrs. $295. Contact: Karnie Starrett, 10840 Queensland St, Los Angeles 90034-3426. (310) 475-1260.

March 13-15—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at US Grant Hotel, San Diego. Fri-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

April 10-11—**The Cutting Edge 1992: Erotic Mysteries—Intimacy, Sexuality and Gender in the '90s.** UCSD at Omni Hotel, San Diego. Fri-Sat. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

April 10-14—**The Power of the Art—Suggestive Therapeutics: An Introduction to Medical Hypnosis.** UCSD at Mission Bay Hilton, San Diego. Fri-Tues. Contact: UCSD.

April 23-24—**11th Annual Conference on Child Abuse and Neglect.** UCDMC at Radisson Hotel, Sacramento. Thurs-Fri. 12 hrs. $175. Contact: UCD.

RADIOLOGY

February 24-28—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI and Interventional.** Stanford University Medical Center at Ritz-Carlton Mauna Lani, Hawaii. Mon-Fri. 23.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 27-29—**Head and Neck Imaging: Total Immersion.** UCSF at Ritz-Carlton, Rancho Mirage. Thurs-Sat. 14 hrs. $325. Contact: UCSF.

February 27-30—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Thurs-Sun. 20 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 2-6—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27.25 hrs. $540. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 11-13—**12th Annual Current Approaches to Radiation Oncology, Biology, and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $375. Contact: UCSF.

March 13-15—**OB/GYN and Abdominal Sonography: Update 1992.** UCSF at Ritz-Carlton, San Francisco. Fri-Sun. 16 hrs. $395. Contact: UCSF.

March 21-23—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. 15 hrs. $350. Contact: UCSF.

March 22-27—**MRI Workshop in Hawaii: 1992.** Queens Medical Center at Kea Lani Hotel, Wailea, Hawaii. Sun-Fri. 37 hrs. $595. Contact: Susan Block, Queens Medical Ctr, 1301 Punchbowl St, Honolulu, HI 96813. (808) 547-4544.

March 23-27—**35th Annual Diagnostic Radiology Postgraduate Course.** UCSF at Fairmont Hotel, San Francisco. Mon-Fri. 35.5 hrs. $595. Contact: UCSF.

March 26-29—**Magnetic Resonance Spectroscopy on In Vivo: Tutorial and Workshop.** Thurs-Sun. 19 hrs. $100-$200. Contact: UCSF.

April 5-10—**Diagnostic Imaging: 1992.** UCSF at Hyatt Regency, Kauai, Hawaii. Sun-Fri. 22.5 hrs. $595. Contact: UCSF.

April 5-10—**General Radiology Review Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sun-Fri. 40 hrs. $425. Contact: UCLA.

April 19-24—**Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $470. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 25—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $125. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

May 4-8—**MRI: A State of the Art Clinical Review.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Mon-Fri. 23.5 hrs. $540. Contact: UCSD.

May 8-10—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 15 hrs. $400. Contact: UCSD.

May 18-22—**Practical Body Imaging: US, CT, and MRI in the 1990s.** UCSF at Marriott's Tenaya Lodge at Yosemite. Mon-Fri. 21 hrs. $595. Contact: UCSF.

May 21-24—**Doppler and Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Thurs-Sun. 21.5 hrs. Contact: UCSD.

June 4-6—**Interventional Hepatobiliary Radiology: Percutaneous Portacaval Shunts, Biliary Stents, Tumor Chemoembolization, Lithotripsy.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17.5 hrs. $425. Contact: UCSF.

June 4-6—**Vascular Stents 1992: A Comprehensive Symposium.** Scripps Clinic and Research Foundation, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 17-19—**Vascular Imaging and Intervention for the '90s.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Fri-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-22—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Mon-Wed. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-24—**Clinical Imaging for the Non-Radiologist.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Quail Lodge, Carmel. Thurs-Sun. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 27-August 1—**Advanced Neuro MRI—Beyond Spin Echo and Musculoskeletal MRI.** Hoag Memorial Hospital Presbyterian at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Sat. 32 hrs. $645. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

March 5-7—**Rehabilitation: Science, Technology, Quality and Costs—Present and Future.** Scripps Memorial Hospital at La Jolla Marriott. 18.5 hrs. $395. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

SLEEP MEDICINE

April 3-4—**Pharmacotherapeutics in Clinical Sleep Medicine.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

SURGERY

February-May 1992—**Temporal Bone Surgical Dissection Courses.** House Ear Institute at Los Angeles. 6 days each. 53 hrs. $1100. Contact: Antonio De la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext 7079.

February 29-March 1—**Renal Transplantation in the 1990s.** Sharp Memorial Hospital at Four Seasons Hotel, Newport Beach. Sat-Sun. 9 hrs. $175. Contact: Sharp Memorial Hospital, 7901 Frost St, San Diego 92123. (619) 541-4530.

March 18-21—**Surgical Challenges in the Head and Neck: A Dissection Course Emphasizing Contemporary Strategies.** UCSD at Basic Science Bldg, La Jolla. Wed-Sat. Contact: UCSD.

March 19-22—**42nd Annual Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: SGS, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

March 26-28—**Symposium on Aesthetic Surgery of the Face.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 18 hrs. $800. Contact: UCSF.

March 29-April 2—**29th Annual Controversial Areas in General Surgery.** UCLA at Hyatt Regency Suites, Palm Springs. Sun-Thurs. 14.5 hrs. $445. Contact: UCLA Extension.

(Continued on Page 156)

How to cure a financial hemorrhage.

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ROY: In 30 years, we've handled all kinds of medical practices. I wish I could say that every one of them was as organized as they were profitable...

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ROY: We're talking in terms of minutes, not weeks or days.

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MARTY: I doubt that there's a doctor out there whose practice wouldn't do better if he or she just had someone on their side, financially speaking. And that should be us. We're good at that.

ROY: Show us last year's tax return and we'll see what you can do to save more – for free.

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Southern California Physicians Only

(Continued from Page 154)

April 2-3—**General Thoracic Surgery.** American College of Chest Physicians at Caesar's Palace Hotel, Las Vegas, Nevada. Thurs-Fri. 13 hrs. $325. Contact: ACCP, PO Box 93826, Chicago, IL 60673. (800) 343-2227.

April 2-4—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. Contact: UCSF.

April 2-4—**12th Annual Meeting and Scientific Sessions of the International Society for Heart Transplantation.** UCSD at San Diego Marriott. Thurs-Sat. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

February 24-28—**Physician Heal Thyself.** UCSD at San Diego Princess Resort. Mon-Fri. Contact: UCSD.

February 28-29—**Nutrition: A Key Partner in the Treatment of Frequently Encountered Medical Problems.** UCD at Walnut Creek. Fri-Sat. Contact: UCD.

March 1-2—**Lactation Educator Training Programs.** UCLA at Loma Linda. 22.5 hrs. $725. Contact: UCLA.

March 12-13—**Dimensions of Caring 1992: Enhancing Quality of Life in Palliative Care.** Scripps Clinic and Research Foundation at Omni Hotel, San Diego. Thurs-Fri. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 2-4—**Medicine Today.** UCSD at Price Center. Thurs-Sat. Contact: UCSD.

April 9-13—**Lactation Educator Training Programs.** UCLA at Westwood. 22.5 hrs. $725. Contact: UCLA.

May 4-7—**The Best Approach 1992: Effective and Efficient Strategies in Pulmonary Medicine, Sports Medicine, Cardiology, Radiology and More.** Group Health Cooperative at Royal Waikoloan, Kohala Coast, Hawaii. Mon-Thurs. 20 hrs. $350. Contact: Group Health Cooperative, CX5, 201 16th Ave East, Seattle, WA 98112. (206) 326-3441.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

February 15-22—**Eighteenth Annual Vail Obstetrics and Gynecology Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 15-22—**Seventeenth Annual Vail Internal Medicine Conference.** Rose Medical Center and University of Colorado School of Medicine at Lion Square Lodge, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 22-29—**Seventeenth Annual Vail General and Vascular Surgery Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 22-29—**Neurology for the Primary Care Physician.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 27—**Perinatal Nursing Update.** University Hospital, Denver. Thurs. Contact: Trish Beachy, (303) 270-8376.

February 28-March 2—**Principles of Anesthesia Technology.** University of Colorado School of Medicine at Marriott Mark Resort, Vail. Fri-Mon. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 29-March 7—**Colorado Review of Anesthesia.** University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 29-March 7—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 29-March 7—**Third Annual Vail Infectious Disease Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 29-March 7—**Colorado Review of Anesthesia.** University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 29-March 7—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 29-March 7—**Third Annual Vail Infectious Disease Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 29-March 7—**Fourteenth Annual Vail Pediatrics Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 1-4—**Twenty-Sixth Annual Conference on the Fetus and Newborn.** Children's Hospital at The Inn at Aspen, Aspen. Sun-Wed. Contact: Jessica A. White, (800) 225-0010 or (303) 861-6946.

March 6-7—**Peripheral Vascular Disease: Noninvasive Diagnosis for Primary Care Physicians.** Medical Education Collaborative at The Westin Tabor Center Hotel, Denver. Fri-Sat. Contact: Laurie E. Christopher, (303) 465-6402 or (800) 442-6632.

March 7-14—**Seventeenth Annual Vail Primary Care Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 7-14—**"Minding the Body, Mending the Mind": Influencing Health and Healing.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 7-14—**Fifteenth Annual Vail Cancer Treatment Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 8-13—**Magnetic Resonance Imaging: Update 1992—Winter Conference.** University of California, San Francisco, School of Medicine, at Marriott's Mark Resort, Vail. Sun-Fri. Contact: (415) 476-5731.

March 12, 19, 26, April 2—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Four consecutive Thursdays. Contact: Trish Beachy, (303) 861-6668.

March 14-21—**Fifteenth Annual Vail Urology Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 14-21—**Fourteenth Annual Vail Sports Medicine Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 15-20—**The Rocky Mountain Vascular Disease Symposium.** Medical Education Collaborative at The Camberley Club Hotel, Beaver Creek Resort. Sun-Fri. Contact: Laurie E. Christopher, (303) 465-6402 or (800) 442-6632.

March 16-19—**Nineteenth Annual Neonatal and Infant Respiratory Symposium.** Ohio State University Hospitals at Marriott Mark Resort, Vail. Mon-Thurs. Contact: Arlene Rogers, Ohio University Hospitals, (614) 293-8487.

March 21-28—**Headache and Facial Pain Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 21-28—**Fourth Annual Colorado Geriatrics Overview/Board Review.** University of Colorado School of Medicine at Iron Horse Resort, Winter Park. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

April 23-26—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

April 25—**Second Annual Women's Health Care Issues Conference.** Children's Hospital at University Hospital, Denver. Sat. Contact: Trish Beachy, (303) 270-8376.

May 4-8—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

May 8-9—**A Caring Affair.** Children's Hospital, Denver. Fri-Sat. Contact: Angela Pollack, (303) 861-6506.

June 12-13—**Fifth Annual Summer in the Mountains Conference.** Children's Hospital of Denver in Gunnison. Fri-Sat. Contact: Mary Haley, (303) 861-6946 or (800) 225-0010.

June 19-20—**Neonatal Resuscitation Course.** Children's Hospital of Denver in Laramie, Wyoming. Fri-Sat. Contact: Lois Pine, (303) 777-7166.

June 23-25—**Community Health Traineeship.** Children's Hospital, Denver. Tues-Thurs. Contact: Pat Winter, (303) 861-6668.

July 9—**Cultural Considerations in Perinatal Nursing.** Children's Hospital at University Hospital, Denver. Thurs. Contact: Trish Beachy, (303) 270-8376.

August 17-21—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

September 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

September 16-17—**Neonatal Resuscitation Hospital-Based Instructor Course.** Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

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September 17, 24, October 1, 8—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Four consecutive Thursdays. Contact: Trish Beachy, (303) 270-8376.

October 23-24—**Fifteenth Annual Perinatal Conference.** Children's Hospital of Denver in Fort Collins. Fri-Sat. Contact: Sharon Adams, (303) 861-6946 or (800) 225-0010.

November 19-22—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

November 30-December 4—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

IDAHO

February 21-23—**33rd Annual Medical Winter Clinics—Wilderness and Travel Medicine.** Ada County Medical Society at Shore Lodge, McCall. Fri-Sun. 9 hrs. Cat. 1. $100 for Idaho Medical Association members; $150, nonmembers. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

March 20—**Idaho Thoracic Society—Annual Medical Symposium.** St Alphonsus Regional Medical Center, Boise. Fri. Contact: Bill Smith, Program Director, Idaho Thoracic Society, 1111 S Orchard, Ste 245, Boise, ID 83705. (208) 344-6567.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 28-29—**20th Annual New Mexico Thoracic Society Lung Disease Conference.** El Dorado Hotel, Santa Fe. Contact: Billie Dytzel, 216 Truman, NE, Albuquerque 87108. (505) 265-0732.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

February 14-18—**Syncope** (Sponsor: UUSM). Fri-Tues. Olympia Hotel, Park City. Contact: UUSM.

February 15-22—**Update in Clinical Microbiology and Immunology** (Sponsor: UUSM). Sat-Sat. Park City. Contact: Midge Beckman, (801) 581-7480.

February 17-21—**Pediatric Emergency Medicine** (Sponsor: UUSM). Mon-Fri. The Marriott, Salt Lake City. Contact: UUSM.

February 19-24—**Physical Medicine and Rehabilitation Update** (Sponsor: UUSM). Wed-Mon. Radisson Inn, Park City. Contact: UUSM.

February 20-21—**Protecting Your Right to Prescribe** (Sponsor: UUSM). Thurs-Fri. University Park Hotel, Salt Lake City. Contact: Sharon Thompsen, (801) 355-7477.

February 23-26—**The 32nd Annual OB/GYN Update** (Sponsor: UUSM). Sun-Wed. Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 26-29—**Infertility and Endocrinology Update** (Sponsor: UUSM). Wed-Sat. Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 28-Mar 3—**The 36th Anesthesiology Update** (Sponsor: UUSM). Fri-Tues. Snowbird. Contact: V. Larsen, (801) 581-6393.

March 2-6—**Microsurgery Workshop** (Sponsor: UUSM). Mon-Fri. University Park Hotel, Salt Lake City. Contact: UUSM.

March 8-14—**Advances in Internal Medicine** (Sponsor: UUSM). Sun-Sat. Snowbird. Contact: UUSM.

March 16-22—**Clinical Cardiac Electrophysiology Board Review** (Sponsor: UUSM). Mon-Sun. Snowbird. Contact: UUSM.

March 24-27—**Family Practice Refresher Course** (Sponsor: UUSM). Tues-Fri. Salt Palace, Salt Lake City. Contact: Leslie Munsee, (801) 581-7234.

June 21-27—**School on Alcoholism, Drug Dependencies** (Sponsor: UUSM). Sun-Sat. U of U Browning Auditorium. Contact: UUSM.

June 24-27—**Slice of Life: Interactive Video and Related Multimedia Technology in Health Education** (Sponsor: UUSM). Wed-Sat. U of U Eccles Genetics Auditorium. Contact: UUSM.

July 12-17—**Update in Internal Medicine Focus on Ambulatory Care Medicine** (Sponsor: UUSM). Sun-Fri. Snowbird. Contact: UUSM.

August 6-8—**ISLD Dental Congress** (Sponsor: UUSM). Tues-Sat. Marriott Hotel, Salt Lake City. Contact: UUSM.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.
WRI:	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

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WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

February 21-22—**Rheumatology in the '90s.** Tacoma. Thurs. Contact: PCMS CME.

February 28—**Office Intervention: Alcohol and Substance Abuse.** Tacoma. Fri. Contact: PCMS.

March 9-13—**Geriatric Board Review.** Seattle. Mon-Fri. Contact: U/W.

March 9-19—**Physical Medicine and Rehabilitation.** Bellevue. Mon-Thurs. Contact: U/W.

March 11—**Medical and Legal Issues.** Everett. Wed. Contact: PNMEI, (206) 258-6322.

March 12-13—**Internal Medicine Review—1992.** Tacoma. Thurs-Fri. Contact: PCMS.

March 20—**Integrated Approach to the Dizzy Patient.** Seattle. Fri. Contact: VMMC.

March 22-25—**Urgent Problems in Primary Care.** Bend, Oregon. Sun-Thurs. Contact: Group Health, (206) 326-3441.

March 23-26—**Death Investigations.** Seattle. Mon-Thurs. Contact: U/W.

March 25—**Ethics Conference.** Seattle. Wed. Contact: VMMC.

March 25-27—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

March 27-28—**Ophthalmology Annual Meeting.** Seattle. Fri-Sat. Contact: WAEPS, (206) 441-9762.

March 30-April 3—**Hawaii and CME.** Kauai, Hawaii. Mon-Fri. Contact: PCMS.

April 8-11—**General Practice Review.** Arizona. Wed-Sat. Contact: PNMEI, (206) 248-6322.

April 10—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

April 10—**Gastro-Esophageal Reflux: A Multi-faceted Disease.** Seattle. Fri. Contact: VMMC.

April 17-18—**Tacoma Surgical Club.** Tacoma. Fri-Sat. Contact: PCMS.

April 24—**Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

April 24-25—**Diabetes of the Eye.** Seattle. Fri-Sat. Contact: U/W.

April 24-25—**Low-Back Pain.** Seattle. Fri-Sat. Contact: VMMC.

April 30-May 2—**Musculoskeletal Disease.** Seattle. Thurs-Sat. Contact: U/W.

May 1-3—**Radiology Annual Meeting.** Seattle. Fri-Sun. Contact: PNWRS, (206) 441-9762.

May 6-9—**Emergency Physicians Annual Scientific Assembly.** Seattle. Wed-Sat. Contact: WACEP, (206) 441-9762.

May 8—**Office Procedures.** Tacoma. Fri. Contact: PCMS.

May 13-15—**Fifth Conference on Occupational Hazards to Health Care Workers.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 15-16—**Medical and Orthopedic Issues of Active and Athletic Women.** Seattle. Fri-Sat. Contact: VMMC.

May 16—**Infectious Disease in Primary Care.** Seattle. Sat. Contact: U/W.

May 21-22—**Cardiology Conference.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

May 27—**Pesticide Medicine.** Eastern Washington. Wed. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 30—**The Fetal Patient.** Seattle. Sat. Contact: VMMC.

June 11—**Endocrinology.** Everett. Thurs. Contact: PNMEI, (206) 258-6322.

June 22-23—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: PCMS.

June 26—**Sports Medicine.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

July 23-26—**Current & Emerging Issues in Cancer Pain.** Seattle. Thurs-Sun. Contact: U/W.

July 29-31—**STD Update.** Seattle. Wed-Fri. Contact: U/W.

August 21-22—**Regional CME Network Meeting.** Seaside, Oregon. Fri-Sat.

September 9-12—**Washington State Medical Association Annual Meeting.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 23-24—**Critical Care.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 11-13—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

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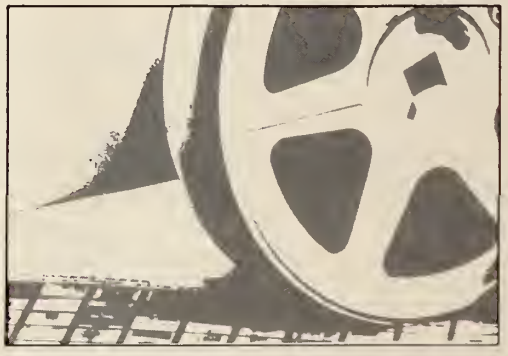

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Symptomatic response to Tagamet therapy does not preclude the presence of a gastric malignancy There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy

Reversible confusional states have been observed on occasion, predominantly in severely ill patients

Tagamet has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole Clinically significant effects have been reported with the warfarin anticoagulants, therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when Tagamet is administered concomitantly Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects

However, a crossover study in healthy subjects receiving either Tagamet 300 mg q.i.d or 800 mg h.s. concomitantly with a 300 mg b.i.d dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older Data beyond ten days are not available (Note All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving Tagamet

A weak antiandrogenic effect has been demonstrated in animals. In human studies, Tagamet has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity

Pregnancy Category B Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Tagamet There are, however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Lack of experience to date precludes recommending Tagamet for use in children under 16 unless anticipated benefits outweigh potential risks, generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported Reversible impotence in patients with pathological hypersecretory disorders receiving Tagamet, particularly in high doses for at least 12 months, has been reported The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population Gynecomastia has been reported in patients treated for one month or longer Decreased white blood cell counts in Tagamet-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported As with some other H_2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia Dose-related increases in serum transaminase have been reported Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving Tagamet has been reported Small, possibly dose-related increases in plasma creatinine have been reported Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely Rare cases of polymyositis have been reported, but no causal relationship has been established Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists Reversible alopecia has been reported very rarely*

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1. Data from randomized, controlled studies. On file, SmithKline Beecham Pharmaceuticals.

2. Palmer RH, Frank WO, Rockhold FW, et al. Cimetidine 800 mg twice daily for healing erosions and ulcers in gastroesophageal reflux disease. *J Clin Gastroenterol* 1990;12(suppl 2):S29-S34

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Articles

Contributions of the History, Physical Examination, and Laboratory Investigation in Making Medical Diagnoses

MICHAEL C. PETERSON, MD, *Morgantown, West Virginia;* JOHN H. HOLBROOK, MD; DE VON HALES, MD; N. LEE SMITH, MD; *and* LARRY V. STAKER, MD, *Salt Lake City, Utah*

We report an attempt to quantitate the relative contributions of the history, physical examination, and laboratory investigation in making medical diagnoses. In this prospective study of 80 medical outpatients with new or previously undiagnosed conditions, internists were asked to list their differential diagnoses and to estimate their confidence in each diagnostic possibility after the history, after the physical examination, and after the laboratory investigation. In 61 patients (76%), the history led to the final diagnosis. The physical examination led to the diagnosis in 10 patients (12%), and the laboratory investigation led to the diagnosis in 9 patients (11%). The internists' confidence in the correct diagnosis increased from 7.1 on a scale of 1 to 10 after the history to 8.2 after the physical examination and 9.3 after the laboratory investigation. These data support the concept that most diagnoses are made from the medical history. The results of physical examination and the laboratory investigation led to fewer diagnoses, but they were instrumental in excluding certain diagnostic possibilities and in increasing the physicians' confidence in their diagnoses.

(Peterson MC, Holbrook JH, Hales D, Smith NL, Staker LV: Contributions of the history, physical examination, and laboratory investigation in making medical diagnoses. West J Med 1992 Feb; 156:163-165)

Arriving at most medical diagnoses requires information obtained from the history, the physical examination, and the laboratory investigation. In 1947 Platt claimed that in most cases the diagnosis can be made with the history alone.[1] In 1975 Hampton and co-workers attempted to evaluate the relative contributions of the history, the physical examination, and laboratory tests in making medical diagnoses in their study of 80 referral patients at a general medicine clinic.[2] Internists were asked to record their presumptive diagnosis, their prediction of management, and their confidence in their diagnosis (or diagnoses) on a scale of 1 to 10 after reading the referral letter and taking the history, after completing the physical examination, and again after completing the laboratory investigation. These diagnoses were compared with those accepted two months after the initial visit. They found that the diagnosis predicted after taking the history agreed with the accepted diagnosis two months after the initial visit in 66 of the 80 patients (82%). The physical examination led to the diagnosis in 7 patients (9%), and the laboratory investigation led to the diagnosis in the other 7 patients (9%).

In a similar study of 630 of his own patients at a clinic with a "cardiological bias," Sandler reported that 56%, 17%, and 23% of his diagnoses were made from the history, physical examination, and laboratory investigation, respectively.[3] Gruppen and associates reported in a study of 119 patients at a primary care walk-in clinic that greater than 90% of their diagnoses were made after the physician heard the chief complaint, read the nurse's intake note, and completed the history taking.[4] In 95% of their patients, the correct diagnosis appeared in the differential diagnosis list after the history was taken.

During the 16 years since the initial study by Hampton and colleagues,[2] there has been a substantial increase in medical technology. In addition, medical school curricula have placed increased emphasis on medical technology while the teaching of bedside skills has languished.

We report here our efforts to quantitate the importance of the history, the physical examination, and the laboratory investigation in making medical diagnoses. This is a prospective study of 80 patients in a general medicine outpatient clinic with new or previously undiagnosed problems using a protocol similar to that used by Hampton and co-workers.[2]

Patients and Methods

All four attending internists at the University of Utah Wasatch Clinics (Salt Lake City) completed standardized questionnaires for 80 general medical outpatients. The patients were nonconsecutive because only those with new or previously undiagnosed conditions were included. Of the 80 patients, 41 (51%) were men; the mean age was 48 years. One was Asian, one was African American, and the rest were white, one being of Hispanic origin. Both physician-referred and self-referred patients were included in the study. In two cases the internist was unable to make a diagnosis and referred these patients to subspecialists; these patients were not included in the study. Seven patients were included in the study more than once for separate medical problems. Five cases of asymptomatic bacteriuria found on routine urinalysis were excluded.

After completing the history, the internists were asked to record their differential diagnosis and their level of confidence for each possible diagnosis on a scale of 1 to 10. Confidence scores always totaled 10, and physicians were allowed to list "don't know" as a diagnosis. As an example, a

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portion of a questionnaire completed for a patient who complained of chest pain could have appeared as follows:

Diagnosis	*Confidence Score*
1. Unstable angina	7
2. Myocardial infarction	2
3. Esophageal spasm	1
	10

After completing the physical examination and again after the laboratory investigation, physicians were asked to list their revised differential diagnosis and a confidence score for each diagnostic possibility they gave as in the example above.

Two months or more after the initial visit, the patient's records were reviewed to see what the accepted diagnosis was at that time. This diagnosis was accepted as the "gold standard" for the purpose of this study.

Confidence intervals were calculated using the commonly accepted formula.[5]*

Results

In 61 of 80 cases (76%, with a 95% confidence interval [CI] of 65.6, 85.9), the leading diagnosis after taking the history agreed with the diagnosis accepted at the time the record was reviewed two months after the initial visit. In 10 cases, after the physical examination was completed, the differential diagnosis was revised so that the leading diagnosis then agreed with the finally accepted diagnosis. In 9 cases, the laboratory investigation led to the finally accepted diagnosis (Table 1).

The mean confidence score for the provisional diagnoses after the history was 7.1, after the physical examination it was 8.2, and after the laboratory investigation it was 9.3. In 70 of 80 cases (88%; 95% CI 79.8, 95.2), the final diagnosis was listed in the differential diagnosis after completing the history.

In 27 of 80 cases, the findings of the physical examination helped to increase the physician's confidence in the diagnosis; in 4 cases, these findings decreased the confidence in the diagnosis. In 22 cases, the results of the laboratory evaluation increased the physician's confidence in the diagnosis; in 1 case, they decreased the confidence in the diagnosis. The types of diagnoses made from the history, the physical examination, and the laboratory investigation are listed in Table 2.

Discussion

This study supports the widely held belief that the "history is the most powerful diagnostic tool available to the internist."[6,7] The narrow 95% confidence interval around the estimate of 76% suggests that chance is not an explanation for these findings. The results of our study agree most closely with those of Hampton and associates,[2] whose study was also completed in a general medicine clinic. Sandler found that the contribution of the history to making medical diagnoses varied considerably with the type of disease being considered. He diagnosed 69% of cardiovascular problems from the history but was able to diagnose only 29% of gastrointestinal problems from the history.

It appears that the history, physical examination, and laboratory investigation are all useful in generating and testing hypotheses. In our study, for example, some of the diagnoses made from the results of the physical examination and laboratory investigation were completely unsuspected after the history was completed. Gruppen and colleagues gave some empiric data to show that the history as well as the physical examination and laboratory investigation are useful in testing and excluding hypotheses.[4]

In our study, as in office practice, it was difficult to separate information obtained from the history, the physical examination, and the laboratory investigation. The physical examination, for example, begins with noticing a patient's general appearance during the history taking. Similarly, the physical examination is not done nor laboratory study results interpreted in a vacuum without already knowing historical points.

*Joseph L. Lyon, MD, MPH, statistically analyzed the data.

TABLE 1.—*The Number and Percentage of Cases Are Given in Which the Final Diagnosis Was Arrived at After the History, the Physical Examination, and the Laboratory Investigation (N=80)*

Type of Evaluation	*Cases in Which Final Diagnosis Made*		*95% CI*
	No.	*(%)*	
History	61	(76)	65.6, 85.9
Physical examination	10	(12)	0, 33.0
Laboratory tests	9	(11)	0, 31.9
Physical examination and laboratory tests	19	(24)	4.6, 42.9

CI = confidence interval

TABLE 2.—*Diagnoses Made From the History, the Physical Examination, and the Laboratory Studies (N=80)*

*Medical Diagnoses**	*Medical Diagnoses**
History	Irregular menses due to birth control pills
Depression (5)	Asthma
General anxiety syndrome (3)	Peptic ulcer disease
Osteoarthritis (2)	Benign leg cramps
Chronic bronchitis (2)	Knee pain due to increased activity
Allergic rhinitis (2)	Spasticity due to CVA
Bursitis (2)	Gilbert's syndrome
Prostatitis (2)	Irregular menses due to menopause onset
Irritable bowel syndrome (2)	Incisional hernia
Panic disorder (2)	Carpal tunnel syndrome
Fatigue (2)	**Physical Examination**
Chest wall pain (2)	Bursitis (2)
Monilial vaginitis (2)	Prostatitis
Hearing loss (2)	Conjunctivitis
Lumbosacral strain or spasm (2)	Myalgia
Urethritis	Abdominal aortic aneurysm
Diabetic neuropathy	Adenopathy (benign)
Esophagitis	Inguinal hernia
Bipolar disorder	Cervical root compression
Labyrinthine dysfunction	Acromioclavicular arthritis
Paroxysmal atrial tachycardia	**Laboratory and X-ray**
Eczema	Benign liver cyst
Congestive heart failure	Trichomonal vaginitis
"Polypharmacy"	Non-A, non-B hepatitis
Tinea cruris	Osteoarthritis
Esophageal reflux	Hemochromatosis
C-6 nerve root compression	Hypothyroidism
Migraine headache	Esophagitis
Tension headache	Hypercholesterolemia
Ruptured posterior tibial tendon	Villous adenoma of the colon
Dementia	
Low back syndrome	
Anxiety	
Exercise-induced asthma	

CVA = cerebrovascular accident

*Numbers in brackets indicate diagnoses that were made more than once.

Several authors have stated that students typically prefer diagnostic tests and broad "search-and-seek" methods in making medical diagnoses,[8,9] whereas experts place more emphasis on the history. Rich and colleagues found that medical residents' perceptions of the history as a useful diagnostic tool increased during their training, perhaps as their interview techniques improved.[7]

Because of the usefulness of the history, we suggest that more time should be devoted to improving history-taking skills during clinical training. For example, trainees should spend more time observing an experienced clinician during an interview and vice versa. In addition, more value should be placed on history taking in terms of reimbursement. This might encourage physicians to develop their interviewing skills more fully and to spend more time talking to their patients.

While the physical examination and the laboratory investigation led to fewer diagnoses than the history in our study, they did help to increase the physicians' confidence in their diagnoses. Another aspect of the usefulness of the laboratory evaluation lies in the normal data that it can provide. For example, a normal coronary angiogram can be helpful in managing a patient with chest pain.

The categorization of some of the diagnoses in Table 2 may seem improbable at first glance. For example, making a diagnosis of monilial vaginitis from the history may seem unlikely. In this situation, the clinician interviewed a woman with diabetes mellitus who had vaginal itching, a perineal rash, and a cheesy discharge but no dysuria. He was able to list the correct diagnosis first on the differential diagnosis list after the history was taken. Similar concerns arose about making the diagnoses of osteoarthritis, Gilbert's syndrome, and paroxysmal atrial tachycardia after the history. Again, careful history taking allowed the physicians to place the correct diagnoses first on the differential diagnosis list.

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HEARD

When she is sewing, Mrs. Dowe can't feel the needle between her finger and thumb. Her doctor says his tests don't show anything. Her best friend's doctor says he can't find any evidence of it and for her simply to ignore it since she can still sew. Her neighbor's doctor says it seems like an odd complaint and he can't find anything wrong with her. Thus, she goes to Dr. Campbell, whom her hairdresser mentions. He says, "Yes, this could be, even though there isn't a test sensitive enough to pick up on it." Since seeing Dr. Campbell, nothing has changed, except that Mrs. Dowe doesn't have a need to mention it to anyone again, and is hardly aware that it even exists.

STEPHANIE MENDEL©
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Articles

Screening and Diagnosis of Alcoholism in the Primary Care Setting

KATHARINE A. BRADLEY, MD, *Seattle, Washington*

As many as 20% of patients seeing their primary physicians may suffer from alcohol abuse and dependence. Often the problem goes unrecognized. In this article I summarize what is known regarding the natural history, risk factors, and available screening techniques for alcoholism. Ultimately, a diagnosis of alcoholism is based on a patient's history, and there are various approaches to obtaining a thorough alcohol history and overcoming patient denial regarding an alcohol problem. Primary physicians have an important role in educating patients about alcoholism.

(Bradley KA: Screening and diagnosis of alcoholism in the primary care setting. West J Med 1992 Feb; 156:166-171)

There is no agreed-on definition of alcoholism. In 1976 the National Council on Alcoholism and the American Medical Association gave the following definition: "A chronic, progressive and potentially fatal disease . . . characterized by tolerance, physical dependence and/or pathological organ changes . . . [as a] consequence of . . . alcohol."[1] Most researchers, however, acknowledge a spectrum of disease, with no clear demarcation between normal and pathologic drinking.

Vaillant performed longitudinal studies of men in Boston, helping to define the spectrum of alcoholism.[2] According to his findings, heavy social drinkers drink about three to five drinks a day and are asymptomatic. Many never have problems, but a significant proportion (10% to 15%) progress to alcohol abuse, defined by the development of symptoms. At this stage, the men usually drink more than seven drinks a day and have social, psychological, medical, legal, and occupational problems related to their drinking. A few persist in this stage, but almost 50% revert to heavy social drinking. The rest, between 25% and 30% of men who abuse alcohol, become alcohol dependent. At this stage, they suffer from withdrawal symptoms and require detoxification. About 3% to 5% of men reach this stage. It is important to note that the amount consumed is not central to these definitions.[2]

The *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R) similarly defines alcohol abuse and dependence along a spectrum of alcohol use (Table 1).[3] A diagnosis of *alcohol dependence* requires at least three of nine manifestations lasting at least a month or recurring repeatedly over a longer time. A diagnosis of *alcohol abuse* requires only the use of alcohol when physically hazardous (item 4) or continued alcohol use despite alcohol-related problems (item 6), with the same time requirements as alcohol dependence. In this article I use these definitions of alcohol abuse and dependence, except when explicitly stated. The term "alcoholism" refers to the entire spectrum of alcohol abuse to dependence.

Prevalence of Alcohol Abuse and Dependence

Alcohol abuse and dependence are common, with their exact prevalence depending on the definition used. The prevalence in the general population is usually assumed to be 5% to 10%.[4] A study by Robins and colleagues of 9,000 households in the St Louis, Missouri; Baltimore, Maryland; and New Haven, Connecticut, areas, however, found a higher prevalence rate of 11.5% to 15.7%.[5] Studies of medical clinic patients have demonstrated a prevalence rate of 11% to 21%.[6-10] Several studies that documented a lower prevalence were not based on interviews but used only self-administered screens.[11,12]

The prevalence of alcoholism in visitors to emergency departments during the day is similar to that in clinics but, according to one study, increases to 29% at night.[13] Patients admitted to hospital have rates of alcoholism between 10% and 50%, with a recent study at Johns Hopkins University (Baltimore, Md) reporting a 25% prevalence of alcohol abuse among medical service inpatients.[14]

Risk Factors for Alcoholism

Gender

Alcoholism is commonly thought to be three to four times more prevalent in men than in women, but data are incomplete.[15] Most studies of alcoholism have been limited to men, and screens commonly used in research were developed based on male populations. The prevalence of alcoholism in women is increasing, and many studies showing a gender difference in the prevalence of alcoholism were completed more than 20 years ago.[16] Nevertheless, the more recent study by Robins and co-workers revealed a fourfold difference between the prevalence of alcohol abuse in men (19% to 29%) and women (4% to 5%) using DSM-III criteria. Alcohol abuse was the most prevalent psychiatric disorder among men 24 to 64 years old but was not among the top four psychiatric diagnoses in women older than 24.[5]

The prevalence of alcoholism among women visiting primary care providers may, however, be greater than that in the general population. Studies of gynecologic practices have found 12% to 16% of patients to be heavy drinkers, suggesting a greater prevalence of alcoholism among women patients than in the female population as a whole.[16] In addition, women who abuse alcohol have more acute and chronic complications of alcohol use than men.[17,18]

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This article is Part 1 of a two-part series. Part 2, "Management of Alcoholism in the Primary Care Setting," will be published in the March 1992 issue.

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ABBREVIATIONS USED IN TEXT

DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised
GGT = γ-glutamyl transferase
MAST = Michigan Alcoholism Screening Test

Ethnicity

Vaillant's longitudinal studies found men of Northern European ancestry—Irish, English, French—to be four to seven times more likely than those of Mediterranean descent—Italian, Jewish, Lebanese, Turkish—to develop alcohol dependence.[2] Native Americans are also at increased risk for alcoholism, although the prevalence rates vary considerably among tribes and abstention is also higher in this population than in the United States population in general. In contrast, Asian Americans and Pacific Islanders as a group have a lower overall risk of having alcoholism than the rest of the US population. Some subgroups, however (such as native Hawaiians, Japanese, and Filipinos), have rates of alcoholism approaching that of the US population as a whole.[19] African Americans and Hispanics both have distinctive patterns of alcohol abuse and dependence but appear to have an overall risk of alcoholism similar to that of the US population at large.[5,19]

Family History

Even when ethnicity is controlled for, family history is a strong predictor of alcohol abuse and dependence, apparently because of an inherited predisposition.[20] Identical twins of alcoholic parents have a greater than 60% concordance rate of alcoholism, whereas the concordance between fraternal twins is only 30%. Adoption studies similarly show that heredity plays a large role in alcoholism; sons of alcoholic persons raised away from their parents have a four times greater risk of alcoholism than controls, whereas sons of nonalcoholic persons raised by alcoholic parents have no increased risk.[21,22] Men with more than one alcoholic parent or two alcoholic relatives appear to be about three times more likely to become alcohol dependent than those with no alcoholic relatives.[2] Blum and colleagues recently reported that a gene on chromosome 11 may confer susceptibility to alcoholism; however, this conclusion has been called into question by subsequent work.[23,24]

TABLE 1.—*Criterio for Alcohol Abuse ond Dependence**

1. Alcohol often taken in larger amounts, or over a longer period, than the person intended
2. Persistent desire, or one or more unsuccessful efforts, to cut down or control alcohol use
3. A great deal of time spent in activities necessary to get alcohol, taking the substance, or recovering from its effects
4. Frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, or home or when alcohol is physically hazardous
5. Important social, occupational, or recreational activities given up or reduced because of alcohol
6. Continued alcohol use despite the knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance
7. Marked tolerance: need for markedly increased amounts of the substance in order to achieve intoxication or the desired effect, or markedly diminished effect with continued use of the same amount
8. Characteristic withdrawal symptoms
9. Alcohol often taken to relieve or avoid withdrawal symptoms

*From *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised.3

TABLE 2.—*Signs ond Symptoms Suggestive of Alcohol Abuse**

Symptoms
Heartburn or gastrointestinal upset
Morning cough or headache, with or without nausea and vomiting
Anxiety, tension, and stress
Insomnia
Concentration or memory deficit

Signs
Tachycardia
Hypertension
Tremor
Purpura or ecchymosis
Palmar erythema
Scars from trauma
Gynecomastia
Hepatic enlargement or abdominal tenderness
Spider nevi
Sensitivity regarding the topic of alcohol

Positive Laboratory Findings
Hyperglycemia
Hyperuricemia
Macrocytosis
Elevated AST level
Elevated HDL-cholesterol level

AST = aspartate aminotransferase, HDL = high-density lipoprotein

*From Davis27 and Holt et al.28

Antisocial Personality

Alcoholism is common in patients with antisocial personality disorder, and Vaillant found boys with behavioral problems in school to be three times more likely to become alcohol dependent than those without such problems.[2] In contrast, psychiatric instability, unhappy childhoods, depression, and anxiety, while possibly increasing the severity of alcoholism, do not appear to be independent risk factors.[2]

Age

In men, heavy drinking usually begins in the teens and 20s, with the highest prevalence of alcohol-related problems occurring in this age group. According to a study by Myers and associates, alcohol abuse continues in 11% to 13% of men aged 25 to 44 years and then appears to decrease, with only 3% to 4% of those older than 65 abusing alcohol.[25] Women apparently begin problem drinking later, but alcoholic complications develop at a similar age in women as in men (in their 40s and 50s) because of a poorly understood telescoping of the disease.[16]

Occupation

Persons who are unemployed or working in occupations that include access to alcohol on the job (bartending), coworker pressure to drink (diplomatic service), minimal supervision (traveling sales), high job stress (professionals), or a lack of routine (writing) may have an increased risk of alcohol abuse and dependence.[26]

Screening for Alcoholism

Many symptoms, signs, and abnormal laboratory values can be clues to the presence of alcoholism (Table 2). Al-

though these findings are neither sensitive nor for the most part specific, they can serve as reminders to consider and screen for alcohol abuse.[27,28]

Quantity and Frequency of Drinking

According to a Rand Corporation study, most patients accurately report their frequency of drinking and the quantity they consume.[29] People who abuse alcohol, however, frequently do not drink daily and underreport the amount they consume when they do drink, making questions about frequency and quantity of alcohol consumed insensitive, although specific, screens. Cyr and Wartman's study of a general medical clinic population with a 20% prevalence of alcohol abuse found that daily drinking was only 34% sensitive and drinking four or more drinks a day was only 46% sensitive for alcohol abuse or dependence.[7] Despite specificities of 94% to 96%, the positive predictive values of these questions were only 59% and 76%, respectively. The negative predictive values, however, were 85% and 87%, respectively.[7]

History of Trauma

Skinner and co-workers found that more than two positive answers to five questions about a history of trauma since age 18 distinguished most alcoholic from nonalcoholic persons (Table 3).[30] The sensitivity and specificity of these questions in a family practice population, however, were only 67% and 70%, respectively.[30] Combining a trauma score with a laboratory screen makes them more sensitive (86%) and specific (83%) but requires a logistic regression, making this approach impractical. Perhaps the most useful findings of Skinner and co-workers for primary care physicians were that injuries from a fight or after drinking had specificities of 91% and 93%, respectively, for alcohol abuse.[30]

CAGE Screen

The CAGE screen (Table 4) comprises four questions taken from the Michigan Alcoholism Screening Test (MAST), a 25-question alcoholism screen used largely in a research setting. Two "yes" answers indicate the presence of alcoholism.[31]

TABLE 3.—*Skinner's Trauma Scale for Alcoholism**

History of Trauma	*Sensitivity, %*	*Specificity, %*
Have you had fractures or dislocations?	88	59
Have you ever been injured in a motor vehicle accident?	59	74
Have you injured your head?	85	76
Have you been injured in an assault or fight?	69	91
Have you been injured after drinking?	88	93

*From Skinner et al.[30]

TABLE 4.—*CAGE Questions**

Have you ever felt you ought to **Cut** down on your drinking?

Have people **Annoyed** you by criticizing your drinking?

Have you ever felt bad or **Guilty** about your drinking?

Have you ever had a drink in the morning (**Eye opener**) to steady your nerves or get rid of a hangover?

*From Mayfield et al.[3]

The CAGE screen is the most commonly recommended screen for alcoholism in the primary care setting because it is short and relatively easy to remember. It has several problems, however. The widely quoted sensitivity of 97% and specificity of 94% are not applicable in outpatient general medical populations because Ewing derived them from a population of extremes: 166 alcoholic men in rehabilitation and 68 nonalcoholic hospitalized men.[32] Ewing's study, therefore, overestimates the screen's sensitivity and specificity in identifying persons who abuse alcohol. In other studies of patients admitted to hospital, a positive CAGE screen has had a sensitivity of 75% to 91% and a specificity of 77% to 96%.[31,33,34]

The CAGE screen has not been prospectively validated in any large primary care population or in women.* In the only large outpatient study of the CAGE screen from Britain, its sensitivity for identifying "excessive drinkers"—more than 35 drinks per week for men and 21 drinks per week for women—was only 55% in men and 35% in women.[35] Moreover, despite its convenience, there is extensive evidence that physicians do not use the CAGE questions,[10,33] and the value of the screen as a self-administered questionnaire is unknown.

When the CAGE screen is used, what does a positive result mean? The predictive value of the screen is dependent on the pretest probability of alcoholism, which in turn depends on its prevalence in the screened population and on an individual patient's risk factors. Assuming a pretest probability of 20% and the sensitivities and specificities described in hospitalized patients, the positive predictive value would be 50% to 82% for two yes answers and 89% for three yes answers. The negative predictive value would be 94% to 97% if two yeses are considered a positive result and 92% if three yeses are required.

Proposed Two-Question Screen

Using the MAST as a gold standard, Cyr and Wartman found that two simple questions, "Have you ever had a drinking problem?" and "When was your last drink?" could identify most alcohol abusers in an outpatient setting.[7] When the response to either question was positive (drinking within the past 24 hours was considered positive), the test had a sensitivity of 92% and a specificity of 90%. In a population of 232 new general medical clinic patients with a 20% prevalence of alcohol abuse, the positive predictive value of this screen was 69% and the negative predictive value was 98%. Subsequent studies of elderly veterans and women, however, have found the test to be less useful in these populations.[36,37]

Other Interview Screening Tests

Additional screening tests for alcoholism have been developed, many derived from the MAST. While they are probably as effective as the CAGE screen, they are more difficult to remember; therefore, they will not be reviewed here.[9,12,38,39]

Laboratory Tests

No good laboratory screen is available for alcohol abuse, although many tests have been studied, including mea-

*Since final acceptance of this article for publication, a large study of outpatients indicates that the sensitivity and specificity of the CAGE in outpatients is indeed comparable to that observed previously in inpatients (Buchsbaum DG, Buchanan RG, Centor RM, Schnoll SH, Lawton MJ: Screening for alcohol abuse using CAGE scores and likelihood ratios. Ann Intern Med 1991; 115:774-777).

surements of mean corpuscular volume, aspartate aminotransferase, γ-glutamyl transferase (GGT), high-density lipoprotein, and uric acid. Of the laboratory tests studied, GGT is the most sensitive and widely available, with a sensitivity of 33% to 54% and a specificity ranging from 76% to 89%.[30,33,34]

Initially, a carbohydrate-deficient form of transferrin was found to be highly sensitive and specific for alcohol abuse.[40,41] In a recent study, however, of a family practice population with a 12% prevalence of "excessive drinking," the transferrin index had a sensitivity of only 45% and a specificity of 89%. The positive predictive value was 50%, and the negative predictive value was 86%. This is as good as available laboratory screens but not better, as had been hoped.[42]

Other proposed biochemical screening tests are platelet monoamine oxidase inhibition by alcohol and adenylate cyclase activity in platelets and lymphocytes. Preliminary findings suggest that when these two tests are combined, they correctly differentiate 75% of alcoholic and nonalcoholic patients. Whether these tests screen for a genetic predisposition to alcohol abuse or for the effects of heavy drinking is not yet clear.[43]

Diagnosing Alcoholism

Given that no gold standard test is available for alcohol abuse or dependence, if screening suggests that a patient has an alcohol problem, the diagnosis must be pursued through additional history taking. The goal of the alcohol history is to encourage patients to talk about any alcohol-related problems they have had, for this is what defines alcohol abuse. A history of withdrawal helps identify patients likely to be alcohol dependent.

Many approaches to an alcohol history have been recommended.[2,44-46] A direct but nonthreatening question, such as "Have you ever in the past thought that you might drink too much?" is often remarkably rewarding. The chronology of the patient's drinking, with special attention to increasing tolerance and alcohol-related problems—motor vehicle accidents or relationship and job difficulties—can also be useful. A question such as "Tell me about when you started drinking and how your drinking pattern has changed since then" can get a patient started. Alternatively, if a patient has answered yes to a CAGE question, an interviewer might seek an explanation: "You mentioned that you had once felt you ought to cut down on your drinking; can you tell me more about that?" If a patient answers yes to the screening question, "Have you ever had an alcohol problem?" the physician might similarly ask "When was that?" and "What sort of problems did you have?" Many other questions, covering all nine criteria of the DSM-III-R, have been recommended in obtaining a full alcohol history. One efficient approach is for the physician or a mental health worker to administer the MAST.

When taking an alcohol history, special attention should be paid to evidence of denial, a fairly specific sign of alcohol abuse. For instance, an alcoholic patient might display inappropriate emotions (such as joking or anger) or might change the topic to avoid discussing an alcohol problem.

Communicating the Diagnosis

Once a clinician determines that a patient has a drinking problem, the diagnosis must be communicated in an explicit yet empathic and hopeful manner.[44,47] The basis of the clinical impression can be explained. Each piece of evidence—the prevalence, the patient's risk factors, suggestive symptoms, positive screening tests, components of the alcohol history, and any signs and laboratory data that suggest the diagnosis—should be included in the discussion.[47]

When communicating a diagnosis of alcoholism, physicians should again expect denial. Some patients will express relief, but many will become anxious, annoyed, amused, or impatient, trying unconsciously to block a discussion of alcoholism. These emotional responses strengthen the likelihood that the original clinical impression was accurate and require that physicians be gentle in presenting a diagnosis of alcoholism while remaining unswayed by the patient's denial. Being hopeful and supportive can help patients confront what is usually a frightening diagnosis,[44] and there is evidence that empathy and optimism on the part of caretakers improve patients' chances for recovery.[48]

Overcoming Denial

If a diagnosis of alcohol abuse or dependence is denied by a patient, several approaches to overcoming denial have been suggested.[44,47] Although controversial, a trial of controlled drinking will often show patients that they are not in control of their drinking. They can be instructed to drink two drinks, no more and no less, every day for three months, with return visits scheduled to discuss their successes and failures.[49] Having a family member present when an alcohol problem is discussed may be helpful, depending on the level of the family member's denial.

Referring patients to an open Alcoholics Anonymous meeting, or recommending that they talk with friends who are members of Alcoholics Anonymous, may help them identify with other alcoholic persons, thereby diminishing their denial. Persons in early stages of alcohol abuse may be unable to identify with those involved with Alcoholics Anonymous, however. Alternatively, alcohol or substance abuse counselors and some psychologists and psychiatrists can help patients confront the diagnosis. The National Council on Alcoholism provides consultations and has offices in many areas. A formal "intervention," a meeting orchestrated by a mental health professional in which persons important to a patient—family, friends, co-workers—confront him or her with the problems resulting from excessive drinking, often forces a patient to acknowledge a drinking problem.[49]

Formal testing using an instrument such as the MAST can provide objective evidence of alcohol-related problems, as can a blood alcohol measurement. Alcohol abuse is considered present if the blood alcohol level is more than 22 nmol per liter (100 mg per dl) in a patient being seen for a general examination, more than 33 nmol per liter (150 mg per dl) in a patient without signs of intoxication, or more than 65 nmol per liter (300 mg per dl) at any time. The blood alcohol level can be estimated by multiplying the osmolality gap by 4.5 (osmolality gap = measured osmolality − [2 × Na + glucose/18 + blood urea nitrogen/2.8]).[50]

Educating Patients

Even when patients deny having alcohol-related problems, providers can educate them about alcoholism and explain that alcoholism is a chronic, treatable disease. Most patients are unaware that the first symptoms of alcohol abuse are usually social problems with relationships, work, or the law, and they can be cautioned to watch for such problems.

Many patients also do not understand that more than 25% of men who abuse alcohol will become alcohol dependent. They can be advised that entering treatment before irreversible social and physical consequences of alcohol abuse occur improves their likelihood of recovery.[51]

Pointing out the strong genetic component to alcohol abuse can help decrease patients' guilt. Physicians can explain that, because of a biologic predisposition, some persons feel the effects of alcohol less, perhaps resulting in their observed inability to know when to stop drinking. Drinking poses an increased risk to them; they may be more apt to become tolerant and subsequently dependent. Therefore, providers can recommend abstinence as a means to prevent progression of the disease.

Physicians can also educate patients about the immediate risks of continued drinking. The fetal alcohol syndrome appears to be dose related, but a safe dose has not been determined. Currently it is the third most frequent cause of birth defects in the United States, affecting 3 of every 1,000 live births annually.[16] Women should be counseled to stop drinking if they are considering becoming pregnant. Patients can also be advised not to drive after drinking[52] and informed of the recently documented risk of swimming while intoxicated.[53] Finally, physicians can stress to patients that heavy drinking will change the way they metabolize drugs. They may suffer from inadequate or toxic drug levels of over-the-counter or prescribed drugs as a result of heavy drinking. Alcohol-abusing patients should be warned about their increased risk of acetaminophen toxicity.[54-56]

Conclusion

Alcoholism is prevalent among patients in primary care settings. Risk factors and screening tests can alert clinicians to possible alcohol-related problems, but a diagnosis of alcohol abuse or dependence should be founded on a thorough alcohol history. When discussing alcohol-related problems with patients, denial should be expected. Scheduling a return visit to readdress an alcohol-related problem is often required to overcome vehement denial. At a minimum, alcohol-abusing patients can be educated about the risks of continued drinking. In this way, practitioners can express their concern and openness and be available when patients want help.

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MEANING MENOPAUSE

My gynecologist calls it
ovarian failure.
I didn't make this up,
nor did he. He learned it
in medical school,
reads it in journals,
says it casually
to his colleagues,
who say it back to him.
Every day he flunks
his patients with it
and they take it on the chin,
but when he serves it
up to me, something snaps.
How funny he looks,
clenching a speculum
in his gloved hand,
trying to calm me
while I shriek like a fury
and challenge him
to evict me in my paper gown.
His eyes travel furtively
to his watch as he recalls
his waiting room
now full to overflowing
with women whose
ovaries are failing
even as they turn the pages
of their magazines. Too bad,
I am going to lie right here,
howling and kicking my feet
on the stirrups
until he recants—this man
so certain of his truth,
whose testicles
know nothing but success.

DORI APPEL©
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Articles

Recognizing and Reporting Adverse Drug Reactions

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Although physicians in practice are most likely to see patients with adverse drug reactions, they may fail to recognize an adverse effect or to attribute it to a drug effect and, when recognized, they may fail to report serious reactions to the US Food and Drug Administration (FDA). To recognize and attribute an adverse event to a drug effect, physicians should review the patient's clinical course, looking at patient risk factors, the known adverse reactions to the suspected drug, and the likelihood of a causal relationship between the drug and the adverse event—based on the temporal relationship, response to stopping or restarting the drug, and whether other factors could explain the reaction. Once an adverse drug reaction has been identified, the patient should be informed and appropriate documentation made in the patient's medical record. Serious known reactions and all reactions to newly released drugs or those not previously known to occur (even if the certainty is low) should be reported to the FDA.

(Lucas LM, Colley CA: Recognizing and reporting adverse drug reactions. West J Med 1991 Feb; 156:172-175)

Although physicians in practice are those most likely to encounter cases of adverse drug reactions, they may fail to recognize them or to attribute an adverse event to a drug effect. Even if recognized as a possible drug reaction, such events are rarely reported. In one study, only 57% of practicing physicians surveyed were familiar with the US Food and Drug Administration's (FDA) voluntary reporting system. Although more than 400 physicians thought that they had detected a serious case of an adverse drug reaction within the past year, only 21 had actually reported it.[1] The purpose of this communication is to review the classification and recognition of these events and to provide practical information on the reporting requirements and process.

Recognizing Adverse Drug Reactions

Adverse drug reactions occur in about 10% of patients admitted to hospital, and 3% to 6% of hospital admissions are related to an adverse drug event. These figures are rough estimates because of the variability in the recognizing and reporting of these events by physicians and are probably low. Comparable data on adverse drug reactions in the outpatient setting are not available. An adverse drug reaction has been defined by the World Health Organization as "one which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."[2] Karch and Lasagna modified this definition to exclude therapeutic failures.[3] The FDA uses a definition that in addition addresses reactions resulting from overdose, drug withdrawal, and therapeutic failures and that may be too broad to be clinically useful.

TABLE 1.—*Severity of Adverse Drug Reactions*

Mild
Does not require treatment or hospital admission or prolong a hospital stay
Moderate
Requires treatment
Requires hospital admission or prolongs a hospital stay by at least a day
Severe
Is life-threatening
Contributes to the death of the patient
Is permanently disabling
Requires admission to a critical care unit
Takes longer than 2 weeks for recovery
Causes a neoplastic process

Adverse drug reactions can be classified according to severity—that is, whether the reaction requires treatment, necessitates hospital admission, or is life-threatening (Table 1). They can also be classified by mechanism: Type A reactions involve exaggerated pharmacologic responses (such as β-blocker–induced congestive heart failure), and type B reactions, which are idiosyncratic and unpredictable based on a drug's pharmacology, may be immunologically mediated (such as carbamazepine-induced thrombocytopenia).

The likelihood that an adverse event is related to drug therapy is classified as definite, probable, possible, or doubtful. The probability classification is based on the temporal relationship of drug administration and the reaction, whether the reaction is a known consequence of the drug, if the reaction resolved on stopping the drug to determine its association with a reaction or recurred with reinstituting the drug to see if the reaction reappears, and if the patient's clinical state could explain the reaction (Table 2). Not all adverse drug reactions fit neatly into one category or another, and clinical judgment is often necessary to determine probability. Various methods for determining the probability of drug reactions have been published. The algorithm developed by Naranjo and colleagues provides a simple method for scoring reaction characteristics and is frequently used.[4] Other more complex methods, such as the method described by Venulet and co-workers, weigh various contributing factors and address concurrent diseases such as renal or hepatic dysfunction.[5] There has been no comparison of these various methods.

Although premarketing clinical trials frequently last several years and involve hundreds of patients, they cannot ensure complete safety of a new drug. Often premarketing trials

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ABBREVIATIONS USED IN TEXT

FDA = US Food and Drug Administration
JCAHO = Joint Commission on Accreditation of Healthcare Organizations

fail to detect serious but rare drug reactions, delayed effects associated with long-term use, adverse effects in selected subgroups of patients (such as geriatric or pediatric populations) or associated with specific diseases, or drug–drug interactions. For these reasons, postmarketing surveillance is essential for both evaluating drugs marketed less than three years—the period during which a drug is termed a new chemical entity by the FDA—and monitoring the frequency of known drug reactions. The single most important way to identify these clinically significant reactions is the recognition and voluntary reporting of them by physicians.

To recognize and attribute an adverse event to a drug effect, physicians should review the patient's clinical course, looking specifically at pertinent characteristics of the patient and drug, as well as the reaction itself, to assess the likelihood of a causal relationship between the drug and the adverse reaction (Table 3). In particular, the patient's concurrent medication, significant medical problems, and risk factors for adverse reactions should be evaluated. The patient's medication regimen should be carefully screened and the patient queried about all medications taken, including over-the-counter and medications "borrowed" from others, to ensure accurate identification of the causative agent. The reaction that occurred should be evaluated in light of the patient's clinical state as well; could the event be explained by known characteristics of the patient's medical illnesses?

Risk factors for adverse drug effects in hospitalized patients include a serious underlying illness or infection, abnormal renal or hepatic function, a previous adverse drug reaction, or multiple drug therapy.[6] Age may not be an independent risk factor but may relate to other factors, such as multiple drug therapy or altered metabolism and excretion of medication. The use of multiple drugs has been the risk factor most strongly and consistently correlated with adverse drug reactions; the rate of such reactions climbs from about 4% in patients receiving 1 to 5 drugs to about 24% in those receiving 11 to 15 medications. It also contributes to drug–drug interactions, which should be ruled out whenever an adverse reaction is suspected. In addition, the use of newly marketed drugs may be a risk factor, as experience with their use is understandably limited compared with drugs in long-term clinical use.

TABLE 2.—*Probability of Adverse Drug Reactions*

Definite
Follows a reasonable temporal sequence after a drug is given or from the time the drug concentration has been established in body fluids or tissues
Follows a well-known response pattern to the suspected drug
Lessens or disappears on stopping the drug (dechallenge)
Reappears if the drug is restarted (rechallenge)

Probable
Follows a reasonable temporal sequence after a drug is administered
Follows a known response pattern to the suspected drug
Lessens or disappears on stopping the drug
Cannot be explained by the patient's underlying clinical state

Possible
Follows a reasonable temporal sequence after a drug is given
Possibly follows a known pattern to the suspected drug
Could be explained by the patient's underlying clinical state or other factors or modes of therapy administered to the patient

Doubtful
Does not follow a reasonable temporal sequence after a drug is given
Can likely be explained by the patient's underlying clinical state or other factors or modes of therapy administered to the patient

TABLE 3.—*Characteristics Helpful in Attributing an Adverse Event to a Drug Effect*

Patient characteristics
Concurrent prescription and nonprescription medications
Serious medical problems
Risk factors for adverse drug reactions, including patient age, serious underlying illness, infection, abnormal renal or hepatic function, previous drug reaction, or multiple drug therapy

Suspected drug reaction characteristics
Drug name or manufacturer
Dosage and duration of therapy
Type of reaction that occurred
Literature or FDA documentation of side effects or adverse reactions to the suspected drug

*Likelihood of a causal relationship between the drug and the adverse event**
Temporal sequence of the reaction following drug administration
Whether the reaction was a known adverse event to the suspected drug
Whether the causal relationship between the reaction and the suspected drug was confirmed by dechallenge or rechallenge; what was the patient outcome
If the reaction could be reasonably explained by known characteristics of the patient's clinical state

FDA = US Food and Drug Administration

*See Table 1 for probability classification.

Once a suspected drug is identified, known adverse reactions to this drug should be reviewed and compared with the type of reaction that occurred and with the clinical result. Certain classes of medications may be more commonly associated with adverse drug reactions. Table 4 lists these drugs along with the types of reactions most frequently reported. After this information is gathered, the probability of the event being an adverse drug reaction can be assessed.

The clinician can facilitate the process of identifying an adverse drug reaction by eliciting information and assistance from pharmacists, pharmaceutical manufacturers, and the FDA and by doing a literature search of case reports and pharmacoepidemiologic studies. Also, similar reactions reported with other drugs in the same or a similar class may be helpful. Pharmacists are often able to identify possible drug reactions, as they may be the first ones contacted about a reaction by either patients in the ambulatory care setting or nurses in hospitals. By screening the medication profile, pharmacists can identify drugs most likely to cause an adverse reaction and can also provide a valuable resource through their access to current drug information. Useful references include Davies's *Textbook of Adverse Drug Reactions*,[7] D'Arcy and Griffin's *Iatrogenic Diseases*,[8] Duke's *Meyler's Side Effects of Drugs*,[9] and the manufacturer's product information, which can be found in the package insert or a current *Physicians' Desk Reference*.[10] The Drugdex Drug Information System, available on microfiche or CD-ROM computer disk, is also a succinct source of information. Pharmaceutical manufacturers provide updated information reported on their products as well.

Example of Adverse Drug Reactions

Case 1

The patient, a 64-year-old man with left lower extremity cellulitis who was allergic to penicillin, had the development

TABLE 4.—*Adverse Drug Reactions Most Frequently Reported*

Drug categories most frequently reported
Antibiotics
Analgesics, including nonsteroidal anti-inflammatory agents
Cardiac drugs
Antihypertensive agents
Asthma drugs
Types of reactions most frequently reported
Dermatologic
Neurologic
Gastrointestinal
Cardiac
Pulmonary
Ear, nose, and throat or mouth

of facial flushing and edema and moderate bronchospasm after receiving 300 mg of vancomycin hydrochloride intravenously over 35 minutes. The infusion was stopped, and intravenous diphenhydramine hydrochloride and methylprednisolone sodium succinate, as well as subcutaneous epinephrine, were administered. The symptoms resolved completely within four hours. This patient had the skin manifestations characteristic of the "red neck syndrome," known to occur with intravenous vancomycin use. The red neck syndrome is directly related to the rate of infusion and most frequently occurs when the drug is infused rapidly, within an hour. The reaction appears to be the result of vasodilation due to the release of histamine. Because of the temporal relationship between administering the drug and the reaction and the pronounced similarity to other previously reported, well-known reactions with the drug, it was considered a definite adverse reaction of moderate severity, despite the fact that a rechallenge was not done.

Case 2

Several hours after receiving 1 gram of vancomycin and 100 mg of gentamicin sulfate intravenously, a 40-year-old man with an infected arteriovenous fistula shunt had a bright red, pruritic, diffuse maculopapular rash develop on his trunk and extremities. The patient had received both drugs a week previously without incident. Despite treatment with intravenous diphenhydramine, the rash worsened and the skin desquamated, requiring a course of oral prednisone before his symptoms resolved. Causality was less clear in this case, in which a reaction developed after two different drugs were given in close temporal proximity. Although allergic reactions manifesting as rash are more common with the use of vancomycin than with gentamicin, a definite association with one agent could not be made, and the reaction was considered a probable adverse reaction of moderate severity to either vancomycin or gentamicin.

Case 3

The patient, a 64-year-old man with hypertension, was prescribed mexiletine hydrochloride for symptomatic ventricular tachycardia. Shortly afterward, he had an episode of excessive blood pressure elevation with readings of 220/115 to 130 mm of mercury, which returned to 122/76 mm of mercury after the drug was discontinued. Two days after rechallenge with mexiletine, his blood pressure again rose to 220/115 mm of mercury and again returned to normal after the drug was stopped. A workup was negative for pheochromocytoma, and mexiletine was investigated as a cause of his hypertension. A review of the literature and consultation with the manufacturer elicited no reports of hypertensive exacerbation or reactions with the use of mexiletine or any other antiarrhythmics. A follow-up of this case revealed several later episodes of comparable blood pressure elevation while off mexiletine therapy. Although his hypertension was closely associated with mexiletine administration, and there was an apparent rechallenge that produced similar results, the labile hypertension later demonstrated by this patient precluded its designation as a definite drug reaction. Because of these doubts and the lack of similar reactions described in the literature, this hypertensive reaction was labeled as a possible adverse drug reaction of moderate severity and was reported to both the drug manufacturer and the FDA.

Reporting Adverse Drug Reactions

Once an adverse drug reaction is identified, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requires that the reaction be documented in the patient's medical chart and that it be reported by the clinician or other health care professional such as a nurse or pharmacist. The JCAHO has required all hospitals to develop a system to summarize adverse drug reactions, to observe for trends that occur in in-hospital patients or outpatients in affiliated clinics, and to conduct ongoing drug utilization monitors. The lack of a reporting system for adverse drug reactions was the second most frequently cited deficiency in hospitals in 1989-1990. Physicians can report such reactions in hospitalized patients to a designated hospital committee—an adverse drug reaction, pharmacy and therapeutics, quality of care, or risk management committee assigned to this function—and hospital pharmacists can assist in this process. The designated hospital committee should then forward appropriate reports to the FDA.

Physicians can also contact the drug manufacturer about a possible adverse drug reaction and receive information on other similar reactions to the suspected drug. Phone numbers for medical information services of pharmaceutical manufacturers are available in the *Physicians' Desk Reference* or through local pharmaceutical representatives. Drug manufacturers are required by law to forward information about possible adverse drug effects to the FDA.

The FDA has a voluntary reporting system for detecting adverse events after a drug has been released for clinical use (postmarketing drug surveillance). Physicians, pharmacists, and even nonhealth professionals can report possible reactions to the FDA directly, and the FDA can provide information on whether similar reactions have been reported previously. It is especially important to report drug reactions in outpatients (as well as in patients in hospital if the hospital's designated committee does not forward its reports to the FDA). An Adverse Reaction Reporting form can be obtained from a local FDA office; a separate form is available for reporting adverse events to vaccines through the FDA's Vaccines Adverse Event Reporting System. Additional information can be obtained from the FDA's national toll-free number, 1-800-638-6725. The voluntary act of reporting cases does not increase physicians' medicolegal liability, as the name of the reporting physician is held in confidence and is not subject to release under the federal Freedom of Information Act.

Physicians should report to the FDA any possible adverse event where there is strong suspicion that a drug involved is producing the event—the physician need not be certain

that the drug is the cause—and when the event is serious (Table 1).

Known reactions that are serious should be reported to the FDA, but all unexpected reactions need to be reported. All reactions to newly released drugs (marketed for less than three years) need to be reported as well. It is not necessary to report therapeutic failures, poisoning or suicide attempts, overdoses due to dosage or administrative error, or a mild reaction not requiring treatment.

Physicians can also submit unusual drug-induced reactions as case reports to medical journals to heighten awareness of a rarely seen or newly recognized adverse drug event. In contrast to single case reports, pharmacoepidemiology, the study of the use and effects of drugs in large numbers of persons, will have an increasing influence on clinical medicine, through both clinical studies of postmarketing drug evaluation and JCAHO-required hospital committees on adverse drug reactions.[1]

Ethical and Medicolegal Implications of Adverse Drug Reactions

Physicians have the responsibility to use their clinical skills to detect adverse drug reactions and then to act on that information. A physician must decide whether an adverse event was indeed a drug reaction, based on the reaction itself and known reactions to the suspected drug; we do not advocate rechallenge in most patients. Readministering a suspected drug when a possible drug reaction has occurred is a decision that a physician must make based on the type and severity of the adverse event and the likelihood that this was a drug reaction. There are no known standards specifically designed to direct physicians in this ethical decision. Once an adverse event has been attributed to a drug reaction, the patient should be informed of it, and JCAHO standards require documenting the reaction in patients' medical records.

For serious drug reactions, documentation in the progress notes is not enough; the information should be listed on a problem list, by a "drug alert" sticker on the chart, or on a computerized medication profile. Reporting the event to the FDA is voluntary; it is the physician's ethical responsibility to learn about the reporting system and how and what to report.

Summary

Physicians should be aware of the potential for adverse drug reactions, especially in high-risk patients, and should be able to attribute an adverse event to a drug effect. Physicians should familiarize themselves with the FDA reporting form, keep a supply on hand, and send a completed form to the FDA to report a suspected drug reaction. If a physician does not have time to report to the hospital, the manufacturer, and the FDA, the FDA should be selected (unless the hospital committee reports drug reactions to the FDA for its physicians). Physicians should be encouraged to report all serious drug reactions, even if the certainty is low, because the FDA will follow up the reports and obtain additional information if it receives a number of reports of suspected reactions of low certainty. Erring on the side of overreporting allows the FDA to assemble the data needed to detect adverse drug reactions. Such reporting, particularly of newly released drugs, is the responsibility of health care professionals in all clinical settings.

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Conferences and Reviews

Acute Renal Failure
Lessons From Pathophysiology

Discussant
JAY H. STEIN, MD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

FLOYD C. RECTOR, JR, MD*: *Much has been learned about the pathogenesis of acute renal failure from research in animal models and in patients with this condition. Our current understanding of the pathophysiology of acute renal failure and the application of this knowledge to therapeutic interventions will be reviewed by Jay H. Stein, MD, Professor and Chair, Department of Medicine, and Dan F. Parman Distinguished Chair in Medicine at the University of Texas Health Science Center, San Antonio.*

JAY H. STEIN, MD†: The topic I shall discuss, acute renal failure, has several possible broad definitions. One that is fairly inclusive is an abrupt, frequently reversible impairment or cessation of renal function that usually is manifested by oliguria or anuria. In the past decade, this definition has been questioned because an increasing number of cases are encountered that are of the nonoliguric type.[1] This broad definition would encompass patients with poststreptococcal glomerulonephritis, crescentic glomerulonephritis, Goodpasture's syndrome, and various tubulointerstitial diseases. In this discussion, however, I focus primarily on that category of diseases frequently identified by the term "acute tubular necrosis." It is important to recognize that this term may not be totally accurate.

To provide an appropriate clinical background for this discussion, I present an illustrative case. Data pertinent to the evolution of the clinical course of the patient are shown in Table 1.

The patient, a 21-year-old man, was admitted to the department of surgery after being shot in the right hip at close range with a shotgun. He was given large volumes of fluids and underwent an exploratory laparotomy at which a right hemicolectomy and an ileostomy were done. Seven days later, he had a right above-the-knee amputation. In spite of massive fluid replacement, the patient had pigmenturia and a progressive rise in serum creatinine levels (Table 1). Eventually, over a five-week period, renal function improved. As can be noted, the patient also had a massive compartment syndrome necessitating amputation.

This patient's course illustrates the classic course of a person with traumatic acute renal failure. I discuss the pathophysiologic basis of the renal functional impairment in this condition and evaluate possible strategies to prevent or attenuate the development of renal failure.

Experimental Models of Acute Renal Failure

No one in clinical practice has had a patient walk into the office who has just taken 10 mg per kg of uranyl nitrate or who has received an intrarenal infusion of norepinephrine. In other words, there has been criticism of the experimental models of acute renal failure that have been studied, some of it justified. Yet, it is obviously difficult to do adequate research studies in very sick patients with acute renal failure. Only the work of Myers and colleagues[2-5] has been of substantial value in the study of this disorder. For the most part,

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TABLE 1.—*Clinical and Labaratary Data in a Patient With Traumatic Acute Renal Failure*

Date	Blood Pressure, mm Hg	Intake liter/24 h	Output liter/24 h	Weight, kg (lb)	BUN mg/dl	CR mg/dl	Urine Myoglobin
8/14	90/60	--	--	--	11.0	1.5	–
8/15	120/80	10.28	4.90	78 (172)	20.0	2.3	+
8/16	122/60	14.50	3.15	82.6 (182)	21.0	2.5	+
8/17	140/70	10.24	4.20	79 (174)	29.0	4.4	+
8/20	150/118	1.15	0.08	--	72.0	8.3	+
8/28	160/70	2.28	0.19	53.5 (118)	105.0	8.1	–
9/8	170/120	1.28	1.32	50 (110)	113.0	8.4	–
9/16	160/114	10.39	10.26	51.3 (113)	60.0	3.1	–
9/18	160/110	7.66	12.08	--	23.0	1.7	–

BUN = blood urea nitrogen, CR = creatinine, + = positive, – = negative

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Reprint requests to Jay H. Stein, MD, Department of Medicine, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr, San Antonio, TX 78284.

however, investigators have relied on various experimental models of the disorder to enhance their knowledge.

It would be reassuring to think that one of the animal models that we study, the glycerol model of acute renal failure, has similarities to the injury seen in the case described here or to patients injured in the bombing of London during World War II[6] or to any other type of crush injury. In the glycerol model, volume depletion, myoglobinuria, hemoglobinuria, and many of the other manifestations seen with trauma are produced. With this in mind, I would like to discuss the experimental work conducted by Reineck and colleagues at the University of Texas, San Antonio, using the glycerol model in rats.[7] The question asked in these studies related to the natural history and reversibility of renal functional impairment in the glycerol model. In other words, is there a phase during which there is a reversible volume-dependent defect, and will this reversible defect be abolished over time? The answer is "yes" on both counts.

Six hours after glycerol has been administered to a group of rats, a large infusion of Ringer's solution causes the restoration of inulin clearance to normal levels (Figure 1).[8] On the other hand, when these animals are given large amounts of fluid 18 hours after they have been given the glycerol, the results are different. Although renal blood flow returns almost to normal (data not shown), inulin clearance returns to only 20% to 25% of normal (Figure 1). The fractional excretion of sodium, which had been low 6 hours after glycerol administration, became notably increased at 18 hours. This is fairly characteristic of some forms of acute renal failure. Some event occurs within 18 hours that changes a reversible, volume-dependent alteration in renal function into fixed acute renal failure.

Factors in the Pathogenesis of Acute Renal Failure

It has been suggested that four major factors are involved in the initiation and maintenance of acute renal failure. These are renal vasoconstriction, tubular obstruction, the leakage of filtrate, and a decrease in glomerular capillary permeability.

Renal Vasoconstriction

Over the years, a great deal of study has been directed toward the hemodynamic alterations that occur in acute renal failure. Extensive studies have evaluated the renin-angiotensin system[9-13] and various other hemodynamic factors that might be involved in the pathophysiology of acute renal failure.[14-17] More recently, endothelin has been suggested as a major factor in the increased renal resistance seen in this disorder.[18] It is important to remember that the effect of ischemic injury in the kidney is unique largely because of the presence of the renal filtration and tubular excretory apparatus. This is well shown by studies in rats in which 30 minutes of ischemia was followed by the restoration of perfusion. Two groups of animals were studied, a control group and a group of animals whose complement had been depleted with cobra venom factor.[19] Complement depletion substantially attenuated the postischemic renal vasoconstriction, but this had no protective effect on the glomerular filtration rate or urinary flow rate (Figure 2).[19] Thus, glomerular filtration could not be restored in these animals, even though renal blood flow was normal in the postocclusive phase. The basis for this phenomenon appears to be tubular obstruction.

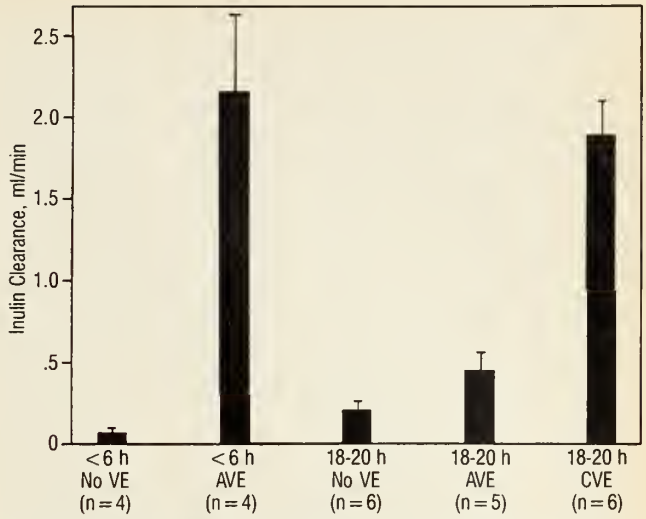

Figure 1.—Inulin clearance is shown for glycerol-treated rats that are volume-expanded (VE) after 6 and 18 hours (from Cushner et al[8]). AVE = acutely volume-expanded, CVE = chronically volume-expanded

Tubular Obstruction

Figure 3 shows the results of the classic study of Arendshorst and co-workers.[20] They measured intratubular pressure in proximal renal tubules in a control setting and one to three hours after renal artery occlusion. Several points were apparent from their results. On observation of the surface of the kidney, most of the tubules were dilated and had debris within their lumina. Figure 3 shows the normal intratubular pressure histogram in the kidney obtained in this study (mean pressure of 10 to 12 mm of mercury). One to three hours after renal artery occlusion, a notable shift to the right had occurred in the curve. Pressures then declined toward normal, although obstruction was still present 24 hours after occlusion. The pressure drop was due to persistent afferent arteriolar constriction, which counterbalanced the increased intratubular pressure.

As cellular ischemia develops in the proximal tubule,

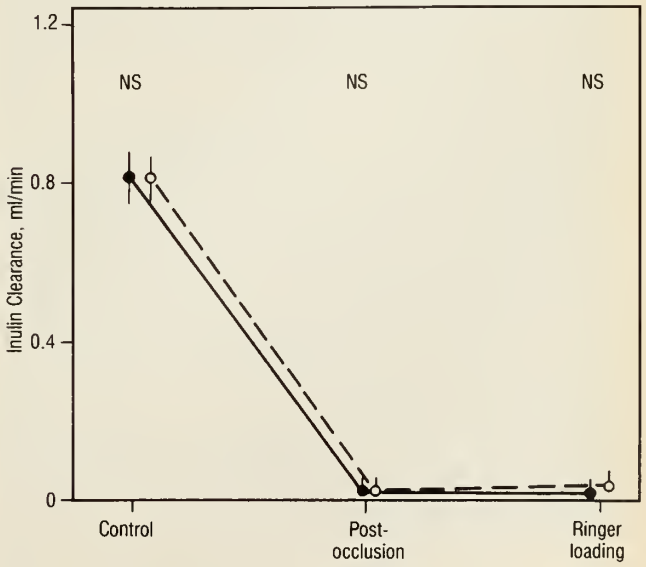

Figure 2.—Complement depletion has little effect on inulin clearance following renal artery occlusion in the rat. Each point represents the mean ± the standard error of the mean of data derived from 10 control animals (●) and 10 animals treated with cobra venom factor (○) (from Stein et al[19]). NS = experimental values do not differ significantly from control values

desquamated brush borders and other debris begin to fill up the tubular lumen and eventually obstruct flow in the straight portion of the proximal tubule. Figure 4 shows the scanning electron microscopic perspective of tubular obstruction in acute renal failure.[21] This is a reproducible and functionally significant consequence of cellular ischemia. Additional perspectives on the role of tubular obstruction in the pathogenesis of the disease are provided by the rat glycerol model. Figure 1 further summarizes studies by Cushner and colleagues at our institution, in which they revisited the issue of the glycerol model and volume repletion.[8] In these experiments, if the animals' volume was continuously expanded after they had been given glycerol, renal function was well maintained. What is the explanation for these data? When the rat kidneys were examined histologically to determine whether a correlation existed with tubular necrosis or cast formation or both in the S3 segment as a function of inulin clearance, no relationship with cell necrosis was found. There was, however, a strong inverse correlation with the magnitude of cast formation (Figure 5). Intratubular pressure data also confirmed this relationship. It seems clear, therefore, that the basic abnormality in the glycerol model relates to tubular obstruction. If intratubular flow were maintained, acute renal failure could be prevented. On the other hand, once cast formation was established, tubular obstruction and fixed acute renal failure would follow.

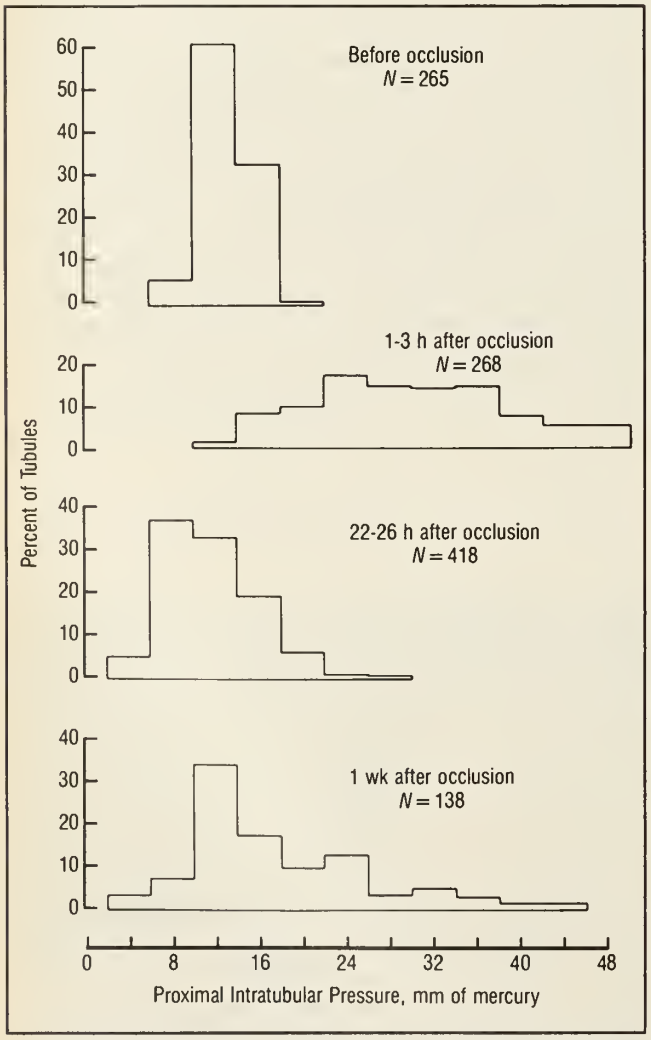

Figure 3.—Notable changes in frequency distributions of proximal intratubular pressure are evident before and after renal artery occlusion (from Arendshorst et al[20]).

I have confined my comments to events in the proximal tubule, but if acute renal failure is studied histologically at later periods after injury, in animals or in humans, most of the casts are present in the distal nephron. Figure 6 shows photomicrographs of two distal tubules and a collecting tubule photographed at the same magnification in a normal rat and in a rat 48 to 72 hours after the onset of acute renal failure.[22] I would propose the following sequence of events in the tubular obstruction of acute renal failure. The proximal tubule, after ischemic injury, begins to restore its brush borders, which contain many enzymes including proteases. These proteases begin to digest the desquamated necrotic cellular material, which eventually winds its way downstream and then combines with Tamm-Horsfall protein,[23] which is made in Henle's loop. This combination of debris and Tamm-Horsfall protein eventually finds its way into the distal nephron and occludes the lumina. A cast occluding the distal tubular system—clearly a strategic location—can cause loss of function of a large number of nephrons.

The mechanism responsible for cast formation has not been studied sufficiently. Bazin and co-workers in Belgium have developed colonies of animals with various light-chain tumors,[24] and Smolens and associates at our institution have done extensive experiments with these tumors and evaluated the development of casts with these various proteins.[25,26] They studied three different light chains with individual isoelectric points (p^I) of 4.3, 5.2, and 6.7. The 6.7-p^I light chain, either in tumor-bearing animals or when given as a pure product to a normal animal, had no effect on renal function (Figure 7). The 4.3- and 5.2-p^I products, on the other hand, had major effects. The 5.2-p^I Bence Jones protein caused cast nephropathy similar to that seen in some patients with multiple myeloma. The 4.3-p^I protein caused some renal functional impairment due to necrosis of the proximal tubule. This protein was a nephrotoxic substance that caused severe tubular necrosis. Alkalinization or acidification of the urine had no effect. Thus, the p^I of these proteins

Figure 4.—The scanning electron micrograph shows a cross section of rat kidney during reflow of blood following release of renal artery occlusion. The lumina of proximal straight tubules (PST) are impacted with membrane-bound blebs of various sizes. (Kidney fixed by vascular perfusion, ultraplaned section; original magnification × 1,400; courtesy of David B. Jones, MD, Department of Pathology, State University of New York, Upstate Medical Center, Syracuse, New York) (from Venkatachalam.[21])

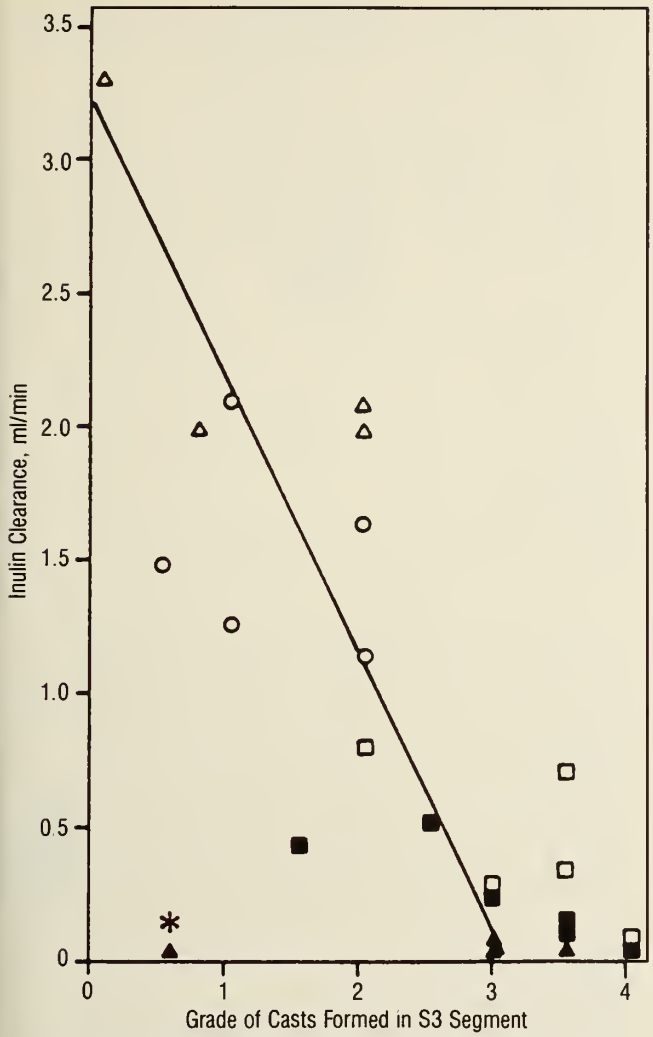

Figure 5.—A strong relationship exists between the degree of cast formation and inulin clearance. This correlation (r = −0.63) is statistically significant ($P < .002$) (from Cushner et al[8]). ▲ = 3 to 6 hours, no volume expansion; △ = 3 to 6 hours, acute volume expansion; ■ = 18 to 20 hours, no volume expansion; □ = 18 to 20 hours, acute volume expansion; ○ = 18 to 20 hours, chronic volume expansion; * = animal had grade 4 cast formation in inner stripe of outer medulla

seemed to be a marker but not the basis for their ability to produce renal functional impairment.

Leakage of Filtrate Across Tubular Epithelium

A third important pathophysiologic mechanism in acute renal failure is the leakage of filtrate across damaged tubular epithelium. My colleagues and I did a simple experiment several years ago to evaluate this process using the technique of microinjecting inulin into the proximal tubule.[27] Normally all of the isotope would be recovered in the urine; after the injection of uranyl nitrate, recovery of the material in the final urine specimen was substantially reduced, suggesting that some inulin was reabsorbed (Figure 8). There are other possible interpretations of these data. For example, Mason and associates argued that microinjecting a substance into a damaged, friable tubule and then applying a high pressure would clearly produce an artifactual leakage of material.[28,29] When Donohoe and associates gave horseradish peroxidase systematically, however, the material still leaked into the interstitium.[30]

The best and most interesting demonstration of leakage of filtrate across damaged tubular epithelium comes from the studies conducted by Myers and co-workers[2-5] in very ill patients with acute renal failure, the disease having developed in many of them after a cardiac bypass procedure. In these studies, the clearance of dextran substantially exceeded the clearance of inulin in patients with overt acute renal failure. The only rational explanation for these findings is that inulin was being reabsorbed across damaged tubular epithelium whereas the larger dextran molecules were not, and that this produced an artifactual change in the ratio. Thus, there can be no doubt that the leakage of filtrate plays an important qualitative role in experimental and clinical acute renal failure. The quantitation of this abnormality, however, is more complex.

Decreased Glomerular Capillary Permeability

Several interesting studies evaluate glomerular capillary permeability in models of experimental acute renal failure.[31-37] Our review of recent studies indicates that either renal ischemia or a nephrotoxic agent can cause a cellular insult, which can subsequently be maintained by prolonged vasoconstriction, the leakage of filtrate, tubular obstruction, or a decrease in glomerular capillary permeability. Most authors are in agreement with this general scheme (Figure 9).[38] Currently the major topic in the field is defining how to alter the cellular insult that occurs in acute renal failure.

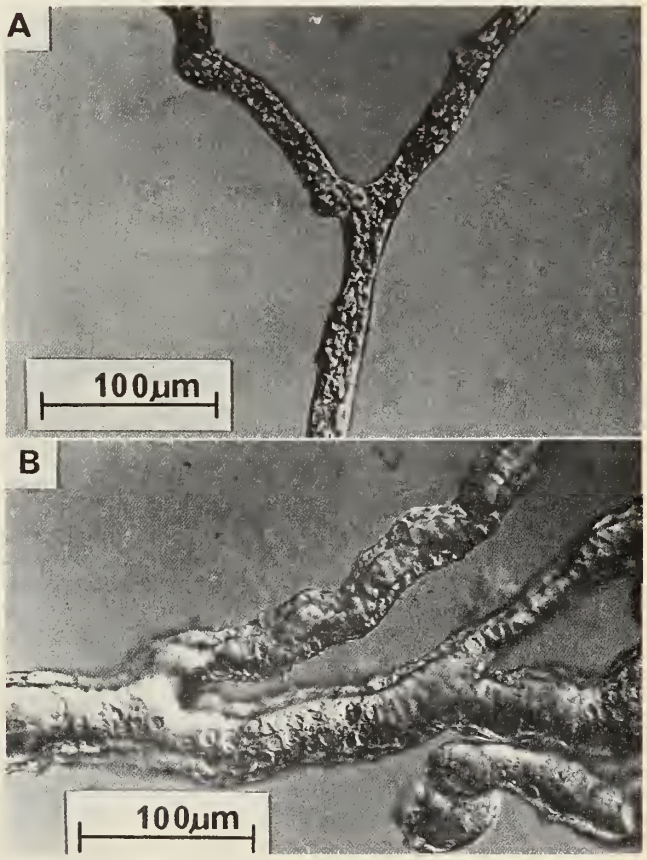

Figure 6.—Collecting and distal tubules were microdissected from control rat kidney (A) and kidney injured by 1 hour of ischemia 24 hours after blood reflow (B). A, The control tubules appear collapsed and are free of luminal obstruction. B, These distal nephron segments from the kidney with acute ischemic renal failure are distended and filled with casts. The tubules were photographed with Normarski differential interference contrast (from Tanner et al[22]).

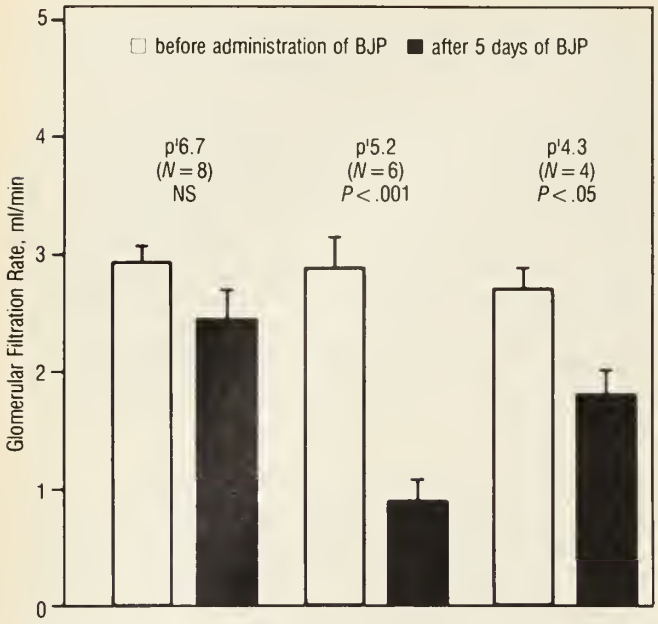

Figure 7.—The graph depicts the effect of the long-term administration of 3 different Bence Jones proteins (BJPs) on the glomerular filtration rate before and after 5 days of administration of 100 mg per day of the BJPs (from Smolens et al[26]).

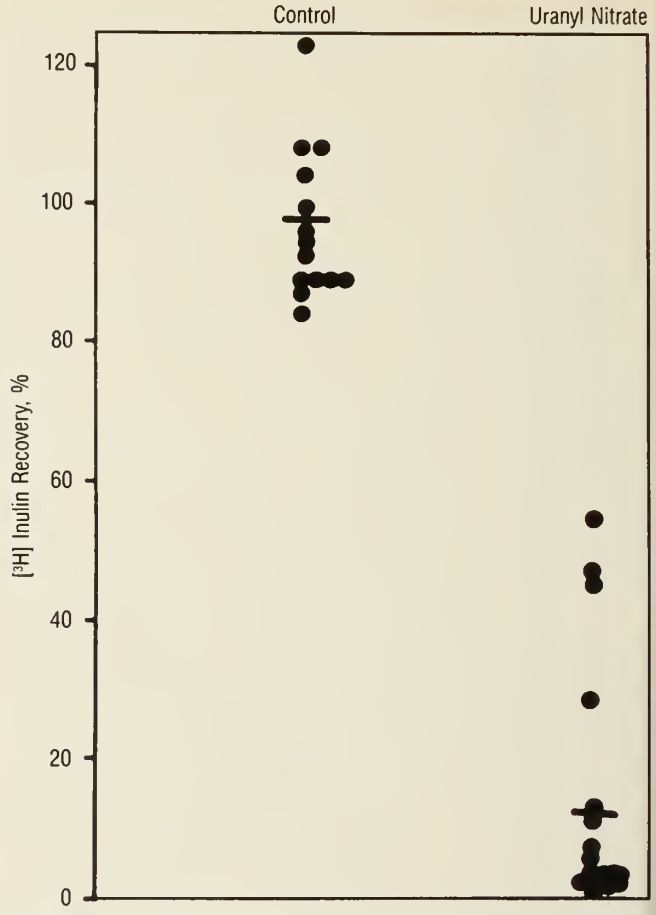

Figure 8.—A summary of [3H]inulin microinjection studies in normal dogs (n = 14) and those given uranyl nitrate (n = 17) suggests that some reabsorption may occur (from Stein et al[27]).

Therapeutic Intervention

Diuretics

The use of diuretics to treat acute renal failure has been a subject of considerable discussion over the past 10 to 15 years. This has included both their mechanism of action and their effect on the course of the disease. Suggested mechanisms of action have included the amelioration of smooth muscle swelling and a reduction of tubular obstruction. The vasodilatory action of these agents and their effect on tubuloglomerular feedback may play a role as well.[39-41]

There is a narrow window of opportunity during which diuretics are efficacious. Figure 10 is taken from an early study,[42] but it remains the best illustration of this point published to date. By administering mannitol from an hour before to about 10 to 15 minutes after an insult to induce acute renal failure, Teschan was able to prevent or attenuate the development of the condition in an animal model. In other words, if our illustrative patient had been shot within the premises of an emergency department and was immediately given mannitol, his renal function may not have deteriorated as readily. It should be emphasized that emergency medical programs stress the importance of giving a large amount of fluids as soon as possible, which may have the same effect as a diuretic.[43] On the other hand, if a patient has trauma and presents 48 hours later, fixed acute renal failure will be present. The only benefit obtained with the use of diuretics at this time is that in some patients it may convert an oliguric to a nonoliguric form of acute renal failure.[44] This is, nevertheless, beneficial because there is much less hyperkalemia, congestive failure, and other problems. As far as prophylactic use is concerned, diuretics are most useful in situations such as cross-clamping of the aorta for aneurysm repair; in this setting they can be extremely effective. In virtually all other situations, diuretic agents cannot be administered soon enough to prevent acute renal failure.

Hanley and Davidson demonstrated in an ischemic model in the rabbit that the use of mannitol would prevent acute renal failure when given before renal artery ischemia (Figure 11).[45,46] There were other interesting points noted in this ischemic model. First, fluid reabsorption was diminished in the proximal tubule. This occurred even where there was no leakage across the proximal tubule. Second, the kidney's ability to pump chloride out of the ascending limb of the loop of Henle of the ischemic tubules was impaired. Further, a form of nephrogenic diabetes insipidus was characterized in the ischemic tubules. There was a marked reduction in the hydro-osmotic effect of antidiuretic hormone in the collecting tubules. Thus, an impairment in solute transport both proximally and in the loop of Henle can readily explain the

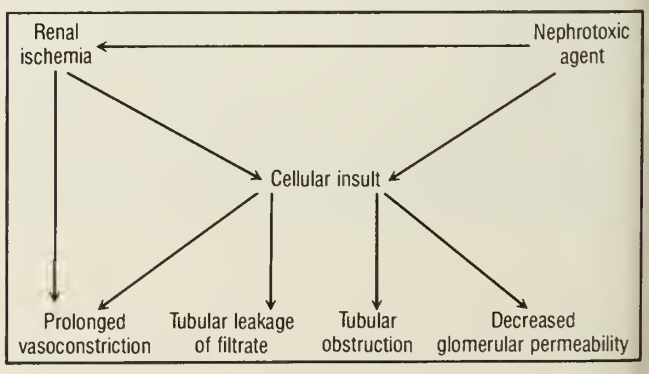

Figure 9.—The schematic diagram depicts the pathogenesis of acute renal failure (from Stein et al[38]).

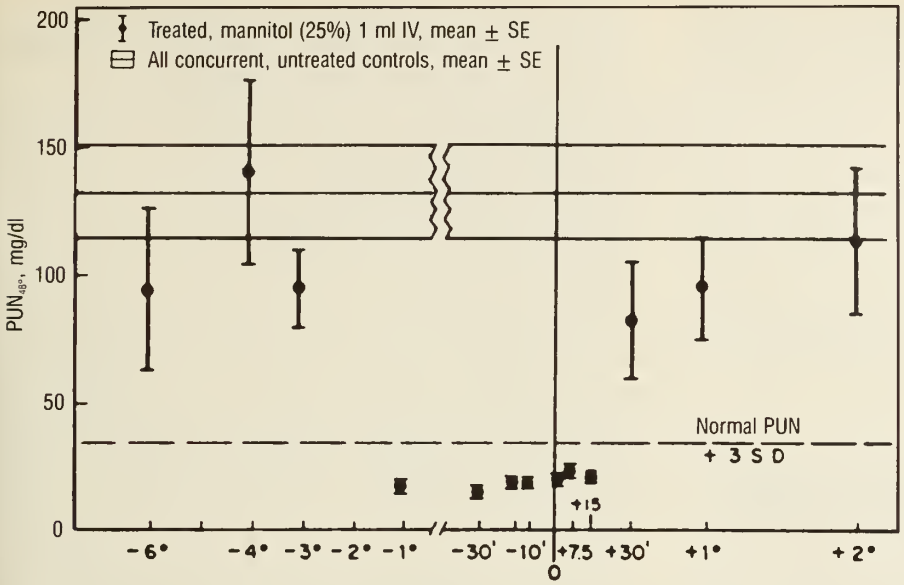

Figure 10.—Plasma urea nitrogen (PUN) levels 48 hours after induction-injection (PUN_{48}) are shown versus the time of treatment relative to attempted induction of acute renal failure at zero time (from Teschan and Lawson[42]). IV = intravenous, SD = standard deviation, SE = standard error [of the mean]

high fractional excretion of sodium and chloride in this setting. Further, the impairment in chloride transport in the loop and the defective response to antidiuretic hormone define the basis for the concentrating defect in acute renal failure. The main difference between the mannitol- and non-mannitol-treated animals was in the proximal tubule where fluid reabsorption was maintained with mannitol. Although the mechanism for this effect of mannitol is unknown, it may be related to an osmotic effect that prevents tubular obstruction, which might then reduce a glomerulotubular feedback mechanism.

Calcium Channel Blockers

Various other protective agents have been suggested in acute renal failure. It has been proposed that an increase in intracellular calcium sets off a cascade of events that lead to irreversible cellular death.[47,48] Agents that block this accumulation of intracellular calcium, such as the calcium channel blockers, might be effective in acute renal failure. There are, however, no convincing clinical or experimental data using these agents to treat acute renal failure.[49-52]

Oxygen Radical Scavengers

Products of oxidant stress may act as mediators of cellular injury in virtually all organs susceptible to ischemia, including the kidney. Regarding the role of free oxygen radicals, there is no question that oxidant stress occurs in the kidney during ischemia.[53,54] Many agents have been used to evaluate protection, however, including glutathione, superoxide dismutase, catalase, deferoxamine mesylate, and allopurinol. At best, functional protection was not consistent in these studies. The evidence that the production of free oxygen radicals is a major determinant of renal functional impairment in acute renal failure is far from convincing.

Adenine Nucleotides

For many years it has been recognized that adenine nucleotides—adenosine triphosphate, diphosphate, or monophosphate—given in vivo could protect against the development of acute renal failure. This has recently been confirmed in vitro by Mandel and associates.[55] This protective effect appears to be greater in normoxic than in hypoxic conditions and is abolished by adenosine deaminase. This may indicate a mechanism by which adenosine gains entry into cells and generates new high-energy phosphate.

Atrial Natriuretic Peptide

Atrial natriuretic peptide is a fascinating substance, but whether it has clinical use remains to be clearly established. A series of interesting studies shows that, if given either before or several hours after an ischemic insult, it has a protective effect in ischemic acute renal failure.[56,57]

Amino Acids

It has recently been shown that glycine or alanine given in large amounts can protect against ischemic injury.[58-60] The viability of proximal tubular cells in culture, as measured by

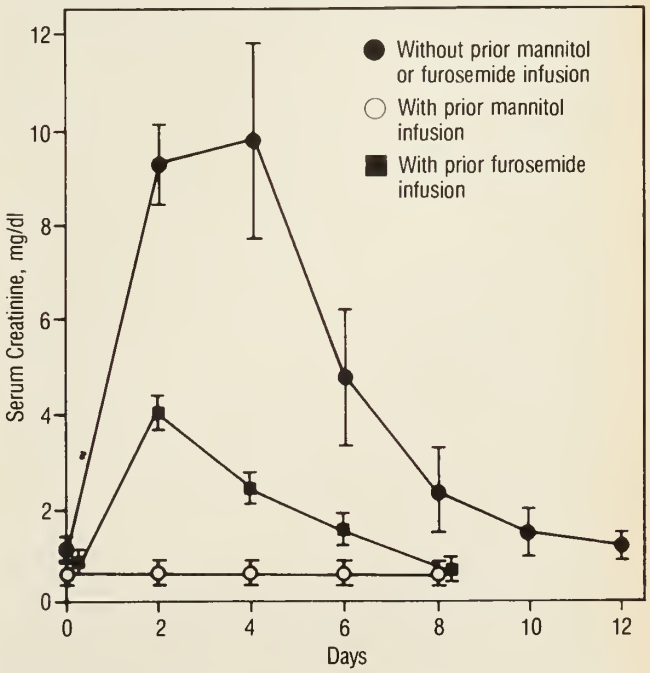

Figure 11.—In a temporal profile of serum creatinine levels in rabbits, 60 minutes of total renal ischemia followed by removal of the opposite kidney produced an elevation of serum creatinine levels that depends on animal pretreatment (from Hanley and Davidson[46]).

the release of lactate dehydrogenase, was notably enhanced in vitro by either glycine or alanine. Although the mechanism of action is unclear, proximal tubular cells treated with either amino acid had a substantial and similar reduction in the level of cellular adenosine triphosphate.

Epidermal Growth Factor

Humes and Coimbra and co-workers have evaluated the effect of epidermal growth factor in acute renal failure.[61,62] They showed that it restored renal function in an ischemic model and a nephrotoxic model of mercuric chloride. An exciting area of future study would be to design approaches that would stimulate growth at the cellular level and thus enhance the reparative process.

Conclusion

I have discussed the pathophysiology of acute renal failure, highlighting the major factors important in the pathogenesis of this condition. An understanding of these factors provides a rational basis for conventional therapeutic interventions, such as volume expansion and diuretic treatment. Furthermore, developments in the area of the cell biology of renal function offer the promise of new, more effective approaches to treating patients who have acute renal failure.

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Cardiac Rehabilitation
Current Status and Future Directions

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Comprehensive cardiac rehabilitation is more than exercise training for patients with coronary artery disease and now includes all aspects of secondary prevention. Exercise training is individually prescribed based on clinical status and therapeutic goals. Smoking cessation and abstinence and the treatment of hypercholesterolemia are integral to the rehabilitation process. Education and counseling are important adjuncts to treatment, especially soon after a coronary event. Vocational rehabilitation can be included simply and effectively in the rehabilitation process. Efficient and cost-effective cardiac rehabilitation is tailored to a patient's medical condition, risk factor evaluation, and vocational status. The future of cardiac rehabilitation will be linked to the success of training nonphysician health professionals to provide preventive services.

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Cardiac rehabilitation had its origins in the 1950s, when the treatment of acute myocardial infarction evolved from three to six weeks of bed rest to "armchair" care and finally to early ambulation.[1,2] When such treatment was shown to be safe,[3] more formal programs of cardiac rehabilitation were developed that emphasized exercise training and vocational rehabilitation.[4] Still, as late as the mid-1970s, a hospital stay of three weeks was common after myocardial infarction. Early exercise testing after myocardial infarction became the standard of care only in the past decade.[5] This rather slow evolution of the care of patients recovering from myocardial infarction has placed the emphasis of cardiac rehabilitation on physical reconditioning after a cardiac event.

In the past decade, advances have occurred in several areas directly related to cardiac rehabilitation. Risk stratification after coronary events allows the early treatment of high-risk patients with medication and revascularization by coronary angioplasty and surgical treatment. Low-risk cases are identified early,[6] allowing comprehensive rehabilitative efforts to be started soon after a coronary event. A careful study of exercise reconditioning programs has led to the development of guidelines that ensure both the safety and efficacy of exercise training for patients with coronary artery disease.[7] Recent data showing that risk factor modification has the potential to slow and even reverse the atherosclerotic process further strengthen a philosophy of secondary prevention for cardiac rehabilitation services. Vocational rehabilitation may be simplified for most patients with coronary disease, allowing a more rapid return to work.[8]

The goals of this article are to review the current status of cardiac rehabilitation services and to offer a perspective on the changing needs for rehabilitation services in the coming years. The anticipated audience is physicians who may refer patients to cardiac rehabilitation programs or provide some rehabilitation services in their practice. Space considerations do not allow this article to serve as a primer for cardiac rehabilitation, but interested readers should understand the concepts of comprehensive cardiac rehabilitation from this article and should be able to expand that knowledge through directed reading.

Goals of Cardiac Rehabilitation

Cardiac rehabilitation may be defined as the process by which patients with cardiac diseases are returned to their optimal physical, psychological, social, emotional, vocational, and economic states. More precise short- and long-term objectives can be defined for cardiac rehabilitation.

Short-term objectives include physical reconditioning sufficient for resuming customary activities, educating patients and family about the disease process, and providing psychological support during the early recovery phase of the illness. Long-term objectives include identifying and treating risk factors that influence the progression of disease, teaching and reinforcing the health behaviors that improve prognosis, optimizing physical conditioning, and facilitating a return to occupational and avocational activities.[8]

Indications for Cardiac Rehabilitation

Cardiac rehabilitation services are generally provided to patients with manifestations of coronary artery disease. In particular, patients recovering from myocardial infarction or a coronary artery bypass operation and those with chronic stable angina are considered candidates. Nevertheless, there is no reason why other patients might not benefit from certain aspects of cardiac rehabilitation services as described later. Reimbursement from insurers and Medicare is generally restricted to patients with coronary artery disease and in some states includes patients recovering from heart transplantation.

Most commonly, patients recovering from uncomplicated myocardial infarction or uncomplicated coronary artery operations are referred for cardiac rehabilitation within three to six weeks of the event. Patients recovering from uncompli-

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TABLE 1.—*Services Provided by or With the Assistance of Cardiac Rehabilitation Programs*

Exercise training
Evaluation and treatment of hypercholesterolemia
Smoking cessation and abstinence
Education and counseling
Vocational rehabilitation
Risk factor surveillance

cated angioplasty and those with stable angina may be referred sooner if they are clinically stable. In general, when a patient is clinically able to perform an exercise test, he or she is ready to begin cardiac rehabilitation.[8]

Rationale for Cardiac Rehabilitation Services

Traditional cardiac rehabilitation programs provide services in three general areas: exercise training, risk factor evaluation, and education and counseling. Other areas that can be offered under the auspices of cardiac rehabilitation include vocational rehabilitation and risk factor treatment (Table 1). Risk factor treatment may involve both medical and behavioral therapies.

Exercise Training

A substantial body of evidence suggests that physical activity provides primary protection from the development of coronary artery disease and favorably influences the prognosis of persons with coronary disease.[9] The Harvard alumni study[10] and the Multiple Risk Factor Intervention Trial results[11] suggest that habitual exercise is inversely associated with cardiovascular mortality. Even low- to moderate-intensity exercise appears to be protective. The risks of exercise in an otherwise healthy population are extremely low, with an estimated annual incidence of 1 cardiac arrest per 7,000 to 18,000 exercisers.[12-14]

Similarly, there is indirect evidence that habitual exercise in patients with coronary disease has a favorable effect on cardiovascular mortality. Several studies of exercise training were done in the past 20 years, only one of which showed a favorable effect on mortality.[15] All studies were limited for a variety of reasons: insufficient sample size, short duration, crossover problems, and a failure to account for other factors possibly influencing mortality, such as β-blocker and aspirin therapy. Two meta-analyses using pooled data on more than 4,000 patients surviving myocardial infarction, however, showed a reduction of overall and cardiovascular mortality by 20% to 25% for those performing regular exercise.[16,17] This magnitude of benefit is similar to that seen in randomized trials of β-blockade after myocardial infarction.[18] In these meta-analyses, there was no significant difference in the nonfatal reinfarction rate for patients randomly assigned to exercise training compared with those in the control group.

Exercise training has important physiologic effects.[19,20] The primary effect is an increase in peak exercise capacity, most commonly expressed clinically in METs (multiples of resting oxygen consumption). One MET—3.5 ml of oxygen uptake per kilogram per minute—is the approximate energy required to stand quietly. Treadmill workloads are commonly expressed in METs. Exercise training increases the MET capacity by 10% to 50%.[21] This increase is primarily mediated through adaptations in skeletal muscle, including increases in capillary density and mitochondrial and oxidative enzyme concentrations. These changes improve oxygen delivery and extraction by exercising skeletal muscle, thus decreasing the cardiovascular requirements of exercise.[22] There is some evidence that exercise programs of higher intensity and longer duration enhance left ventricular function,[23] perhaps through improved perfusion.[24]

Clinically, the effects of exercise training include lower resting and submaximal pulse rates and systolic blood pressures and increased maximal MET capacity.[20] These changes occur across all subsets of patients with coronary artery disease, including those with evidence of myocardial ischemia[21,25] and left ventricular dysfunction.[26,27] Although ischemia generally occurs at the same double product, increased skeletal muscle efficiency allows a greater level of work to be done before ischemia is manifested. The greatest effects generally occur in those patients most limited at the time exercise training is initiated. Other related benefits of exercise include improved lipid profiles,[28,29] improved blood pressure control in hypertensive patients,[30-32] and improved psychological profiles including increases in self-efficacy (to be described later).[33,34]

Evaluation and Treatment of Hypercholesterolemia

Substantial basic and clinical data link elevated serum cholesterol levels to clinical manifestations of coronary artery disease. In the past decade, clinical trials have shown that lowering serum cholesterol levels has a beneficial effect on cardiovascular morbidity and mortality in persons without symptomatic coronary disease.[35-37] More recent data from several studies suggest that lowering serum cholesterol levels in patients with symptomatic coronary artery disease slows the progression of coronary atherosclerosis in the majority of cases.[38] The status of coronary atherosclerosis was evaluated using serial coronary angiograms, with computer-assisted quantitation of luminal diameters in most studies.[39-41] Two studies also showed a significant reduction in symptomatic coronary events in treated patients compared with the control groups.[40,41] These studies have also shown for the first time that coronary atherosclerosis can be reversed in some patients. Thus, aggressive dietary and drug management of hypercholesterolemia is strongly indicated in patients referred for cardiac rehabilitation.[42]

Smoking Cessation and Abstinence

Cigarette smoking increases the risk of manifestations of coronary artery disease developing and of recurrent complications occurring after coronary symptoms develop.[43] Stopping smoking lowers the primary risk of myocardial infarction to nearly that of nonsmoking within three years.[44,45] Smoking cessation and abstinence after myocardial infarction halves the risk of a recurrent coronary event in the first year. In addition to diminishing the cardiovascular risk, smoking cessation also favorably influences the risk from other diseases including several cancers, peptic ulcer disease, and chronic lung disease.[43] These data suggest that smoking abstinence programs should be incorporated into standard cardiac rehabilitation.[8,46,47]

Behavioral Treatments

Although type A behavior is regarded as a risk factor for the development of coronary disease,[48] controversy exists regarding its specific role. Type A behavior is characterized by three primary features—time urgency, competitive

achievement striving, and hostility. Only the last is thought to have a detrimental coronary effect.[49] The influence of type A behavior on the prognosis of symptomatic coronary disease is also controversial.[50-52] A single study suggests that specific therapy to modify type A behavior reduces the risk of cardiac death and nonfatal myocardial infarction in men with a history of myocardial infarction.[53] Although other disabling psychological problems, such as depression and anxiety, should be treated in patients referred to cardiac rehabilitation programs, the evidence that specific interventions for type A behavior are beneficial is not strong.

Other Risk Factors

There is no clear evidence that the aggressive treatment of hypertension, obesity, and diabetes mellitus influences the prognosis in patients with symptomatic coronary artery disease. A lack of data in these important areas should not deter physicians from providing optimal treatment of these well-established risk factors. Cardiac rehabilitation programs can assist in the management of these problems by providing close surveillance of blood pressure, weight, and glucose control at the time of regularly scheduled exercise sessions.[54]

Education and Counseling

Education and counseling are integral parts of most cardiac rehabilitation programs and show promise in enhancing quality of life, especially in the early recovery phases of myocardial infarction.[55] There are, however, few data to substantiate long-term beneficial effects on psychological outcome by these interventions.[54] One area in which cardiac rehabilitation has a well-established beneficial effect is in improved self-efficacy.[55] "Self-efficacy" is a psychological term describing how a person's judgment regarding his or her capacity to do a task is an important determinant of whether the task will be attempted. Self-efficacy is a measure of self-confidence and is a useful tool in developing and establishing healthy behaviors, such as exercising, dieting, and smoking abstinence. Specific techniques for increasing self-efficacy have been developed and can be helpful within the context of promoting healthy behaviors.[8,55]

Vocational Rehabilitation

The cost of cardiovascular disease is high, estimated at $85 billion annually for direct treatment costs alone. The cost of resulting short- and long-term disability is substantially higher, estimated at three to four times the direct costs of care. These indirect costs result from goods and services not provided due to cardiovascular disability. The indirect costs can be reduced by increasing the number of patients with cardiovascular disease returning to work and shortening the interval between a cardiac illness and return to work. Demographic, medical, and psychological factors all influence whether a patient works after a cardiac event. Age, work history, and job type are the most important demographic factors. The severity of the cardiac illness is the most important medical factor. Patients' perception of their health and the advice treating physicians give regarding reemployment are the most important psychosocial factors.[8]

In patients recovering from uncomplicated myocardial infarction, early exercise testing and specific advice regarding return to work shortened the interval from 75 to 51 days in a randomized trial.[56] More than 75% of working patients younger than 60 years can return to work earlier than is commonly allowed. Similar guidelines are probably applicable to patients recovering from uncomplicated coronary bypass grafting. Substantial financial benefits accrue to patients and employers as a result of shortening the interval between a cardiac event and return to work. A work evaluation can be easily incorporated into standard rehabilitative care.

Organizing Cardiac Rehabilitation Services

Inpatient Cardiac Rehabilitation

The cardiac rehabilitation process usually begins during a hospital stay for myocardial infarction, unstable angina, or coronary revascularization by angioplasty or bypass procedure. With the shortening of hospital stays for all cardiac treatments, the goals of inpatient cardiac rehabilitation should be limited to the most important areas. These important goals include providing a structured progressive ambulation program so that patients will be physically able to perform customary activities at home; teaching patients to recognize important cardiac symptoms and to take appropriate action; maintaining smoking abstinence; teaching patients the doses, effects, and side effects of their medications; instructing patients in how to obtain routine and emergency medical care; and providing basic information about the outpatient rehabilitation process.

Effective inpatient cardiac rehabilitation programs are multidisciplinary. They usually involve nurses, physicians, physical therapists, nutritionists, and exercise physiologists. Coordinated programs of mobilization and education are sufficient to meet the basic needs of most patients.[8] The concepts of risk factor modification should be introduced in the hospital, especially the continued abstinence from smoking. Patients who have been admitted to hospital have a limited capacity to retain new information, however. Therefore, most efforts of secondary prevention should be deferred to the outpatient program.

Outpatient Cardiac Rehabilitation

Comprehensive standards for traditional outpatient rehabilitation programs have recently been published.[7,8,57-61] These specific guidelines should be incorporated into all existing and new outpatient programs to ensure a safe, efficacious, and consistent approach to cardiac rehabilitation. Several specific services may be offered by outpatient programs.

Exercise training. Structured exercise sessions are the hallmark of outpatient cardiac rehabilitation. A symptom-limited exercise test is the basis for the exercise prescription. Patients without evidence of angina or asymptomatic ischemia, congestive heart failure, or electrical instability are usu-

TABLE 2.—*Increased Risk for Exercise Training in Patients Who Should Receive Greater Surveillance During Exercise Training or Who Should Not Exercise*

Pathophysiology	*Manifestation*
Left ventricular dysfunction	Congestive heart failure; ejection fraction < 30%; history of cardiogenic shock
Myocardial ischemia	Angina pectoris; exercise-induced ST depression; severe coronary artery disease
Ventricular arrhythmias	Complex arrhythmia at rest; complex arrhythmia during exercise; history of sudden cardiac arrest

ally good candidates for symptom-limited testing. The exercise test will establish the patient's MET capacity and guide the development of a rational exercise prescription. In some patients it will identify high-risk characteristics that require further diagnostic evaluation or therapeutic interventions. The test also identifies cases in which exercise training is safe but should be done in more carefully monitored settings (Table 2). The exercise test is especially important in the modern era of thrombolytic therapy and early coronary interventions to be certain that occult myocardial ischemia and electrical instability are not present.

The fundamental concepts of exercise training of patients with cardiac disease are well described.[7] Exercise training effects are related to the FIT principle: frequency, intensity, and time. Most cardiac exercise programs provide three sessions a week for 12 weeks. The intensity of exercise training is best prescribed as a percentage of the peak heart rate attained on symptom-limited exercise testing. Conservative target heart rates are prescribed initially to ensure that patients can complete the exercise session safely without excessive fatigue. The time of each session varies between 30 and 90 minutes. Patients monitor their exercise by their pulse rate.

In patients without important contraindications, exercise training is safe. A national survey of cardiac rehabilitation programs estimated the rate per 1 million patient hours of exercise of fatal events at 1.3, of myocardial infarction at 3.4, and of resuscitated cardiac arrest at 8.9.[62] Patients at higher risk require more intensive surveillance, including continuous electrocardiographic monitoring during training. Patients at lower risk can exercise in a supervised setting using pulse counting and intermittent electrocardiographic monitoring for surveillance. All programs should have resuscitation equipment immediately available, and the staff must be trained in advanced cardiac life support procedures.

As patients improve with exercise training, their prescriptions may be advanced by increasing the target heart rate and by adding exercise sessions at home. The same techniques for self-monitoring pulse rate and symptoms must be used in home exercise, so patients must be competent in these techniques before home exercise is recommended.[8,63-65]

Risk factor evaluation. Patients entering cardiac rehabilitation should have their risk factors assessed at entry. These include blood pressure, fasting lipid and glucose levels, weight, smoking status, and stress levels. Goals should be individually tailored for each patient. The patient should have a clear understanding of the goals and how they might be accomplished. Specific guidelines for evaluating hypercholesterolemia are available through the National Cholesterol Education Program.[42]

Risk factor treatment. Risk factor treatment is an area where cardiac rehabilitation programs and primary physicians should coordinate their efforts. In many respects, the cardiac rehabilitation program is an ideal setting for risk factor treatment. Most of the issues related to long-term health-related behavioral change require frequent visits, time-consuming face-to-face interactions, social and professional support, and access to nonphysician health care professionals such as nutritionists and nurses. A cardiac rehabilitation program that provides 36 one-hour sessions over 12 weeks can incorporate techniques for educating patients, enhancing and monitoring compliance, and establishing social support systems. In contrast to the physician's office, where visits are usually infrequent and brief, in a cardiac rehabilitation program, healthy behaviors can be introduced, molded, and reinforced more effectively.

TABLE 3.—*Treatment Thresholds and Goals for Patients With Coronary Artery Disease**

Cholesterol	*Threshold, mmol/liter (mg/dl)*	*Goal, mmol/liter (mg/dl)*	*Treatment Form*
Low-density lipoprotein...	≥3.36 (130)	≤3.36 (130)	Dietary
Low-density lipoprotein...	≥4.14 (160)	≤3.36 (130)	Drug

*From the National Cholesterol Education Program.[42]

Specific guidelines for cholesterol management have been published (Table 3).[42] Dietary management can be facilitated with the help of a nutritionist for both individual and group teaching. Drug therapy is effective if dietary treatment is insufficient for reaching the goals of reducing low-density-lipoprotein cholesterol levels. Exercise training can raise the high-density-lipoprotein cholesterol values. Smoking abstinence can be facilitated by individual or group programs and reinforced during exercise sessions. The use of nicotine polacrilex can improve the short- and long-term abstinence rates. Stress reduction can also be accomplished by group and individual treatment. Stress reduction commonly occurs as a byproduct of regular exercise sessions.

Education and counseling. Most cardiac rehabilitation programs provide group education that addresses a variety of topics. Sessions are usually open to both patients and family. The education focuses on those areas relevant to the long-term management of coronary artery disease. Possible topics include basic pathophysiology, treatment options, diet, cholesterol evaluation and treatment, medication effects and side effects, stress management, and other topics of interest to the group. Informal social support groups are often formed by patients and can be beneficial to them and their families in the early recovery period after a cardiac illness.

Vocational rehabilitation. Because most working patients younger than 60 years will return to work after a cardiac event,[55] complex vocational rehabilitation is necessary for only a few patients. Occasionally patients cannot return to the same job after a cardiac event because of a medical complication, such as stroke or severe congestive heart failure, that makes them incapable of doing the work. A small number of patients are legally restricted from returning to their previous job, such as pilots and public safety workers. In these circumstances, which mandate a change of job, specialized vocational rehabilitation services are indicated.

The majority of patients recovering from uncomplicated myocardial infarction or a coronary bypass procedure can return to work earlier than is commonly recommended. The average patient with no complications has a functional capacity of 7 to 8 METs within a month of the illness. This capacity is sufficient to perform most jobs, including those with moderate physical requirements. In the case of jobs requiring higher levels of physical activity, exercise training can usually bring the physical capacity to a sufficient level. In the absence of signs of a poor prognosis, such as substantial left ventricular dysfunction or myocardial ischemia, most patients can return to work within 30 to 40 days of their cardiac illness. The symptom-limited exercise test done before entry into a cardiac rehabilitation program may be used to substantiate a good prognosis, assess the functional capacity, and aid

the physician and cardiac rehabilitation team in providing specific guidelines for a return to work.[8]

Future Directions in Cardiac Rehabilitation

Traditional efforts in cardiac rehabilitation that have emphasized exercise training will be replaced by a more comprehensive approach to secondary prevention in the coronary population. While exercise clearly benefits patients with coronary disease, aggressive treatment of other risk factors improves prognosis as well.

The process of cardiac rehabilitation begins with risk stratification to identify and treat abnormalities of left ventricular dysfunction, myocardial ischemia, and electrical instability. Once these important prognostic factors are evaluated and treated, secondary prevention measures should begin. These include exercise training, smoking cessation and abstinence, cholesterol evaluation and treatment, stress management, vocational rehabilitation, and education.

Currently only 15% of all patients eligible for cardiac rehabilitation services enroll in formal cardiac rehabilitation programs. Formal programs, which are generally supervised by nurses, exercise physiologists, and other nonphysician health professionals, do not yet completely address the comprehensive approach outlined here. The future of cardiac rehabilitation must include more coordinated efforts between physicians and rehabilitation programs if cardiac rehabilitation is to meet these standards. Systems must be developed whereby all patients with coronary artery disease can benefit from comprehensive programs of secondary prevention that are individually prescribed. Multidisciplinary teams of nonphysician health professionals offer the greatest potential for providing the breadth of preventive services necessary to accomplish the goals outlined here. Ultimately, primary and secondary prevention is the most cost-effective means of improving prognosis in coronary heart disease.[66,67]

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HERMAN KATTLOVE IS OUR ONCOLOGIST

After fifteen years, Herman and I talk of art—
    Georgia O'Keefe and Degas
and travel and cities we love—
    Berlin and Paris
our grown children and what they are doing.

Dr. Kattlove and Shelley talk of drugs—
  Megace and tamoxifen
of therapies—radiation and chemo
  and experimental treatments.

Herman tells me to come back in six months
(A year is too long, he'd miss me.)
He tells Shelley to come back in a month—or less.

Shelley and I talk of art and travel
  and favorite cities.
She tells me of her treatments.
  I remember mine.
I wonder when Shelley and Herman will discuss
  Bali and Vienna?
  Andrew Wyeth and Van Gogh?

MARY KAY CROWTHER©
Long Beach, California

Epitomes

Important Advances in Clinical Medicine

Dermatology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in dermatology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Dermatology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Current Concerns With Collagen for Soft Tissue Augmentation

THE MOST FREQUENTLY USED approved product for soft tissue augmentation over the past decade is, without doubt, collagen (Zyderm, Zyplast). Nearly half a million patients have been treated to date for a variety of problems, including wrinkles, scars, and cosmetic correction. "Collagen" is essentially a purified soluble form of predominantly bovine type I dermal collagen. The product is rendered minimally antigenic during the manufacturing process when the telopeptide ends of the collagen molecules are cleaved using enzymatic digestion. Zyderm I and II differ only in their final collagen concentration (35 mg per ml and 65 mg per ml, respectively). Zyplast, however, is a gluteraldehyde cross-linked form of this processed collagen.

Recently a great deal of controversy has surrounded the use of injectable collagen for soft tissue augmentation. Issues of concern include the overall safety of the device, a questionable association with connective tissue diseases, and indications for the product's use. Treatment site reactions occur in 1% to 4% of patients with nonreactive skin tests. Local hypersensitivity reactions, including erythema, induration, and possibly pruritus, are by far the most common. These reactions usually occur within four weeks of injection, and the probability of such a reaction decreases with subsequent treatments over time. Topical steroids, antihistamines, and the like are of questionable benefit, but fortunately the process is self-limiting.

Two far less common but important complications include abscess formation and local necrosis. Abscess formation appears to be a manifestation of a more prominent hypersensitivity reaction that results in clinically unmistakable necrosis with localized pain and swelling. The severity can vary, and only one of several injection sites may be involved. Treatment consists of drainage or intralesional steroid therapy. In contrast, local necrosis is most likely a vaso-occlusive phenomenon caused by vessel compression or obstruction with the material. The process is often heralded by an instantaneous cyanotic or blanching pattern within the area of treatment. The glabella is by far the most common area for necrosis, especially when deeper dermal injections are used, as with Zyplast. Accidental interarterial placement of the material can cause embolism, and a case of partial vision loss caused by ophthalmic artery emboli has been reported. This risk can be minimized by proper administration and site selection.

Questions regarding the possible linkage of injectable collagen use and connective tissue disease have been asked since the product's inception. Serial antigenic challenge with a foreign protein can theoretically cause problems. In fact, a model for a rheumatoid arthritis-like illness has been described in rats repeatedly challenged with human type II collagen. Challenge with type I or III collagen, however, did not lead to disease in this model. To date, about 100 cases of dermatomyositis, polymyositis, and lupus associated with collagen injection disease have been reported. The US Food and Drug Administration (FDA) recently required Collagen Corporation to revise labeling to reflect a "higher-than-expected" incidence of two rare autoimmune diseases—polymyositis and dermatomyositis—among patients treated with collagen injections. Studies have not established a causal relationship, however. Similarly, no correlation or cross-reactivity between any human collagen antibodies and those of the implant material has been established.

To limit this potential, although an unproven risk, patients with underlying connective tissue diseases should not receive this treatment. Double skin testing may also be used to assess patients with possible sensitivity. Such a skin testing technique will also minimize the incidence of the more common hypersensitivity treatment reactions.

Finally, FDA indications for which collagen is approved include scar and wrinkle correction. Uses for other types of cosmetic corrections including earlobe and lip augmentation may be implied but are not listed as specific indications for this product.

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Tattoo Removal Using the Ruby Laser

DECORATIVE TATTOOS have almost certainly existed since prehistoric times. Because social customs and individual preferences change, patients frequently seek information concerning the removal of these marks. Despite having a large number of techniques to choose from including salabrasion, chemical scarification, dermabrasion, infrared coagulation, split-thickness tangential excision, cryosurgery, excisional surgery, and ablation using the argon and carbon dioxide lasers, there has been no ideal form of treatment available. Furthermore, many of these techniques shared the common problems of incomplete pigment removal, considerable postoperative wound care, prolonged healing, permanent hypopigmentation, textural changes, and scarring. As a result, newer techniques have been eagerly awaited that might allow a more satisfactory management of patients with tattoos.

With the recent Food and Drug Administration approval of the ruby laser, the wait for an ideal form of treating tattoos may finally be over. Developed in the early 1960s, the ruby laser was the first functional laser system. Despite early publication regarding its use in the treatment of decorative tattoos, it was not until 1983 that reports reappeared describing the beneficial effects of ruby laser therapy. It now appears from several published large series of patients that this technique offers some distinct advantages over alternative forms of therapy for tattoos. The most important benefit is the ability to remove tattoos without scarring. This apparently is possible because the high-intensity red light produced by the ruby laser is selectively absorbed by the blue and black carbon particles found in amateur and professional tattoos. In addition, the energy is emitted to the pigmented tissues without damaging the surrounding normal skin. This concept, known as selective photothermolysis, has also been recently employed with a dye laser for the treatment of port-wine stain birthmarks in infants and young children without scarring. Additional benefits include minimal postoperative care and rapid healing.

This technique does have some limitations. Presumably because of differences in the size of pigment particles and variable energy absorption by the metals used to produce tattoo colors, all patients do not respond uniformly to ruby laser therapy. In general, blue and black tattoos respond the best, but even yellow, green, and red will usually fade with multiple treatments, which are performed at five- to six-week intervals. Typically, more treatments will be required for professional tattoos than for amateur tattoos, but an accurate prediction cannot be made for the ultimate response or the number of treatments that will be required. Anesthesia may be needed in about 50% of patients, especially when the tattoos are on sensitive areas such as the fingers, breast, or face. Despite these problems, the benefits resulting from this technique are substantial. It should be considered for patients with tattoos in anatomic locations that are susceptible to poor healing or for those who are seeking the best cosmetic result possible.

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Skin Cancer and Sunscreens

NONMELANOMA SKIN CANCERS, basal cell carcinomas, and squamous cell carcinomas are by far the most common cancers that occur in the United States each year. They make up 30% to 40% of all malignant growths. The incidence of nonmelanoma skin cancers has been increasing progressively in the past several decades.

Malignant melanoma, the third most common skin cancer, accounted for 3% of all reported cancers in the US in 1990, and it was estimated that there would be 32,000 new patients with melanomas and that 6,200 persons would die because of this cancer in 1991. The melanoma incidence has been increasing at an alarming rate for at least the past four decades.

The role of the sun in inducing nonmelanoma skin cancers is well established. There is also epidemiologic and experimental evidence indicating that sun exposure most likely stimulates melanoma formation.

The avoidance of sun damage should be the mainstay of a preventive medicine approach to limiting all three of these skin cancers. The use of sun blocks and sunscreens is probably useful in preventing chronic sun damage. Sun blocks reflect and scatter the offending rays. They provide excellent protective coats but are usually cosmetically unacceptable.

In contrast, sunscreens absorb the injurious rays and can be applied in cosmetically acceptable invisible films. They are labeled with a sun-protective factor (SPF) number that represents the hours of exposure to the midday sun required to induce a minimal erythema dose (MED) through the sunscreen divided by the MED without the sunscreen in place. This is a measure of UVB protection. Everyone who is going to be in the sun should wear a sunscreen with a SPF of at least 15.

UVB rays make up the primary action spectrum for the sunburn erythema, chronic sun damage, and skin cancer. Although recent studies indicate that UVA radiation can also cause a delayed erythema in human skin, it requires much more energy. A person could receive 15 or more UVB-induced MEDs in a summer's day but only get 2 to 4 UVA-induced MEDs in that same day.

In humans, UVA augments the acute sunburn effects of UVB. In experimental models, UVA acts additively with UVB-induced cancer formation, and, with large enough amounts, UVA can by itself induce cancers. It would therefore seem prudent to protect against UVA as well as UVB damage.

Recent advances have included increased SPF, UVA protection, and substantivity (water resistance). Sunscreens with SPF values as high as 50 are available. In one study, it was shown that a sunscreen with an SPF of 29 prevented the UVB damage that 15 MEDs induced through a sunscreen with an SPF of 15. A potential drawback is that the increased concentration of chemicals might lead to increased contact irritancy and allergic sensitization. UVA protection has been accomplished by increasing the percentage of certain molecules, such as the benzophenones, or by adding certain specific UVA-absorbing compounds, such as butyl-methoxydibenzoylmethane (Parsol 1789). Micronized particles or melanin may be incorporated to increase UVA protection.

The third advance has been in products that resist being removed by swimming, perspiring, or even by rubbing. It is still a good idea to reapply a sunscreen after swimming or

vigorous exercise to ensure protection. In general, reapplication two to four times throughout a day in the sun is wise. The recent fear of a few sunscreens containing carcinogens has not been confirmed.

In summary, there are excellent practical medications that prevent acute and chronic sun damage. The challenge is to convince people to use them.

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Autologous Skin Grafts for Leg Ulcers

CULTURED EPITHELIAL AUTOGRAFTS, a technique in which skin taken from the patient is expanded in the laboratory, show great promise in treating acute and chronic wounds. First used to treat extensive burns, epithelial autografts are now applied to chronic wounds such as decubitus and leg ulcers.

This method takes advantage of existing technology for culturing skin cells, or keratinocytes. A small skin biopsy is taken and cultured, and the cells multiply to form epidermal sheets several thousand times the area of the original biopsy. An initial 1-cm² specimen of skin can expand to cover large, denuded areas. On the day of grafting, the sheets are detached from their culture flasks, placed on Vaseline gauzes, and stapled or sutured to the area to be covered. The success of the grafting procedure depends on a meticulous preparation of the recipient bed and on immobilization of the grafted site because any shearing force will interfere with the graft's attachment.

There are several advantages to this technique. First, the donor site is much smaller than that needed for conventional grafting, and, because some cells are stored, it is possible to graft a second time without a second donor site. Second, the cosmetic appearance of these grafts is often superior to conventional grafts. Finally, cultured skin grafts relieve pain in chronic wounds, and the grafts themselves may promote healing through autocrine function.

Cultured epithelial autografts enable clinicians to treat large wounds using a small donor site. These grafts have been successfully used to treat acute wounds such as burns and chronic wounds such as leg ulcers. At facilities across the country, this technique shows great potential in promoting wound healing.

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Advances in Local Anesthesia

THE COMMONLY USED amide anesthetics, such as lidocaine, have been associated with pain on infiltration. Although the mechanism is unknown, it has been suggested that the acid pH used to stabilize the lidocaine, and more so the epinephrine, is the reason for the discomfort. Studies adding 1 ml of 8.4% sodium bicarbonate to 10 ml of lidocaine hydrochloride with or without epinephrine show a statistically significant decrease in the pain of infiltration, with no compromise in onset, duration, and extent of anesthetic efficacy. Other studies have confirmed that unbuffered anesthetic, freshly prepared buffered lidocaine with epinephrine, and week-old buffered material do not differ in anesthesia or vasoconstriction.

In addition, the search continues for an effective and safe topical anesthetic that is relatively nonsensitizing. In the US, a combination of tetracaine hydrochloride 0.5%, adrenaline 0.05%, and cocaine 11.8% has become increasingly popular in pretreating wounds to decrease the pain of suturing and local anesthetics. The main drawback is limited absorption through intact skin. While there has not been sufficient absorption of cocaine to cause euphoria or other systemic symptoms, there is enough to cause urine screening tests to be positive for cocaine for as long as 48 hours. This may represent a problem in an era of random testing in our society. This should be stocked as a prepared solution in emergency departments and other hospital pharmacies.

A topical combination anesthetic recommended for intact skin—a eutectic mixture of local anesthetics (EMLA)—has been available for use in Europe for several years. It is a combination of 2.5% lidocaine hydrochloride and 2.5% prilocaine hydrochloride, both long available as injectable and topically applied preparations. Studies have shown it to be 95% effective in creating superficial local anesthesia when used properly. Its limitations are that it requires about an hour under occlusion to reach this level of effectiveness, and the anesthesia is superficial. Reports have shown it to be adequate for argon laser, split-thickness skin grafts, and curettage of molluscum contagiosum. It also decreases the pain of the needle stick of local anesthetics and, in combination with buffered lidocaine, may be of real help. Some early work done with topical amethocaine shows it also to be a safe and effective topical anesthetic when applied under occlusion for 30 minutes.

In summary, several alternatives are or will soon be available for local anesthesia in anxious or difficult-to-treat patients.

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Bacillary Angiomatosis

SEVERAL PREVIOUSLY UNNOTICED opportunistic infections have come to light during the course of the current human immunodeficiency virus (HIV) epidemic, most notably oral hairy leukoplakia and bacillary angiomatosis. The latter, a

new opportunistic infection, was first described when small, apparently gram-negative bacilli were noted on electron microscopic examination of a cutaneous lesion suspected of being Kaposi's sarcoma.

Cutaneous bacillary angiomatosis, sometimes called epithelioid angiomatosis, is marked by red papules and nodules and, less often, rounded subcutaneous masses. On a biopsy specimen, there is a proliferation of capillaries with greatly protuberant endothelial cells. The lesions may easily be mistaken for pyogenic granulomas, Kaposi's sarcoma, or angiosarcoma. Features that enable a specific diagnosis of bacillary angiomatosis to be made include numerous neutrophils, nuclear dust, and purplish granular material that proves, on electron microscopy or Warthin-Starry stain, to consist of bacteria. Most patients respond well to a regimen of erythromycin, 2 grams per day.

Recent attention has focused on the identity of the causative bacillus and on the spectrum of internal disease produced by the organism. Because the agent of bacillary angiomatosis causes vascular proliferation, there has been speculation that it is related to *Bartonella bacilliformis*, which causes an acute febrile illness known as Oroya fever and a chronic illness with numerous cutaneous vascular lesions known as verruga peruana. Recent studies using whole cell fatty acid chromatography have shown that the agent of bacillary angiomatosis has a similar profile to *Bartonella* species. Because some of the original patients had been scratched by cats and because the bacillus shows the same restricted staining pattern as does the bacillus of cat-scratch disease, the proposal has been made that bacillary angiomatosis is caused by the cat-scratch disease bacillus. This remains unproved. So far, culturing the bacillus using conditions favoring growth of the cat-scratch disease bacillus has proved difficult. A third possibility has been established by molecular biologic studies. Sequencing of the 16S RNA gene has shown that the agent of bacillary angiomatosis is most similar to a rickettsia, *Rochalimaea quintana*, the agent of trench fever, which is clinically unlike bacillary angiomatosis.

The spectrum of internal disease caused by this organism, with or without cutaneous lesions, has expanded. Soft tissue masses, lymphadenopathy, and dramatic hepatomegaly and splenomegaly have been seen in affected patients. Peliosis hepatis (the formation of blood-filled cysts in the liver) is an unusual consequence of infection. Clusters of bacilli inhabit the connective tissue that rims these cysts. The internal manifestations of bacillary angiomatosis also respond to antibiotic therapy. Fatal untreated cases have occurred.

The next few years will doubtless see more precise identification of the organism, as well as the documentation of additional cases in non–HIV-infected patients.

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Suntan Parlors—A New Hazard to Health

With the development during the past 20 years of high-intensity lamps emitting UVA, the suntan facility industry has burgeoned. In California, it is estimated that there are about 2,000 such facilities.

UVA is long-wave ultraviolet light in the range of 320 to 400 nm. Unlike UVB (280 to 320 nm), it passes through window glass. It is present throughout the day and during the entire year. UVA penetrates the epidermis into the dermis. Because of this, it can damage not only the Langerhans cells in the basal layer of the epidermis but also collagen tissue, the lens and retina of the eye, and even blood vessels. A growing body of literature indicates the potential for the development of basal and squamous cell carcinomas, as well as the development of cutaneous melanomas on the basis of exposure to UVA.

Beginning in the 1980s, it was noted that an increasing number of eye injuries were caused by exposure to UVA in suntan facilities. Severe burning of the skin, exacerbation of autoimmune illnesses such as lupus erythematosus, photoallergic reactions of the skin, premature aging of the skin, an increase in the number of skin cancers, and one death have been reported. The use of suntan parlors apparently contributed to an epidemic of phytophotodermatitis among grocery workers handling fresh produce and fresh flowers.

It is hoped that an awareness of the hazards of UVA will lead to decreased exposure to this harmful agent.

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Carbon Dioxide Laser Treatment of Actinic Cheilitis

Actinic cheilitis is a diffuse premalignant change of the lip caused by long-term sun exposure and possibly aggravated by the use of tobacco products. Clinically it consists of a whitened, thin epithelium with or without fissures and slow-to-heal erosions. It may look and feel like "chapping," but it is found almost exclusively on the lower lip, which receives more ultraviolet exposure than the upper lip because it protrudes forward and is oriented upward. This parallels the 10:1 increased incidence of an invasive malignant lesion on the lower lip compared with the upper lip.

The carbon dioxide laser is well suited to precisely remove this premalignant epithelium with less morbidity and lower recurrence rates than other available techniques, such as liquid nitrogen, topical fluorouracil, tretinoin (Retin-A), and vermilionectomy with mucosal advancement flap repair.

The vermilion border is marked and the entire vermilion infiltrated with local anesthetic to smooth its surface, which may be preceded by a submental block or topical mucosal anesthetic to ease the pain of injection. The carbon dioxide

laser is used in a defocused mode, usually from 2 to 4 W and at a size of between 2 and 4 mm in diameter. One or more passes with the laser are made until the entire lower lip has a mottled white-pink appearance. This procedure is done as much by feel and experience as anything else. Small areas that retain a rough surface can be precisely vaporized to attain a uniform appearance. There is no blood loss and minimal early postoperative pain because nerves and blood vessels are sealed by the laser. Postoperative care consists of peroxide compresses and antibiotic ointment applied several times a day until the wound is fully epithelialized in 7 to 14 days.

Before laser therapy is undertaken, a biopsy should be taken from any ulcerated or indurated (firm) areas to exclude invasive squamous cell carcinoma. Clinical or pathologic examination may also be required to exclude lichen planus, contact dermatitis, and discoid lupus erythematosus before such treatment.

Carbon dioxide laser treatment of actinic cheilitis is an efficient, office-based procedure that results in minimal scarring and a lower recurrence rate than other destructive therapies. It offers cost savings and fewer complications than vermilionectomy and mucosal advancement. The removal of premalignant changes of the lip can be expected to reduce the occurrence of potentially metastasizing labial squamous cell carcinomas.

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Treatment of Scabies and Similar Infestations

SCABIES CONTINUES TO BE a source of substantial discomfort in our society. The typical infestation is acquired by direct contact with the *Sarcoptes scabiei*. The female mite burrows and lays her eggs in thin keratinized epithelium. Intense nocturnal pruritus develops in most patients about three weeks after contracting the initial infestation, due to an allergic or irritant response to the mite's secretions. Classic areas of distribution for the linear burrows include the web spaces of the fingers, toes, axillae, groin, and waist. A vigorous immunologic reaction to the mite may cause widespread skin eruption, with few typical burrows. In addition, young children and elderly patients may have involvement of the palms, soles, scalp, and face. Immunocompromised patients, especially those infected with the human immunodeficiency virus, are more susceptible and may even have Norwegian scabies marked by hyperkeratotic lesions and numerous mites.

Skin scraping is the only consistent means of detecting these mites and evaluating treatment. Any unexplained pruritic skin lesions should be scraped and examined by potassium hydroxide wet mount or with mineral oil under a microscope to look for the mite, fecal debris, and eggs contained in the burrow. In rare cases, a biopsy is required to establish an accurate diagnosis, especially for Norwegian scabies.

The following important principles are used in treating patients with scabies:

- Prescribe a limited amount of a suitable medication;
- Avoid overtreatment;
- Treat the whole body from neck to toes. In infants and debilitated, bedridden patients, the head and face also require treatment;
- All household contacts (and frequent visitors) need to be treated simultaneously;
- Give detailed verbal and written instructions;
- Patient should launder underclothing and bedding after completion of treatment and not use again for three days;
- Do a follow-up inspection at one and four weeks;
- Always recheck and rescrape patients if any lesions persist; and
- Caution patients that no matter what treatment is provided, the itching will commonly persist for several weeks after adequate treatment.

Lindane (1% γ-benzene hexachloride [Kwell]) has been until recently the standard scabicide in the US because of its efficacy and cosmetic acceptability. Lindane displays some toxicity, which may include serious neurotoxicity. Although most reported cases have involved overexposure or mishandling, risks of such events must be considered when the drug is provided. There have also been reports of resistance to lindane in California, which has prompted the California Department of Health to recommend alternative therapies.

Permethrin 5% cream has recently been introduced as a highly effective and novel scabicide, that may largely replace lindane for the treatment of scabies. Permethrin is a photostable synthetic pyrethroid with potent insecticidal activity and low mammalian toxicity. The 5% permethrin cream has been used successfully in heavily infested communities in which scabies had been endemic. Permethrin cream has a lower potential for neurotoxicity and may be preferable for the treatment of scabies, particularly in young children. Because controlled studies are lacking in children younger than 2 months and pregnant women, permethrin is still not recommended for these patients. The major disadvantage of this drug is its cost, being 10 to 12 times as expensive as lindane.

Other scabicides include crotamiton (Eurax), which is not very effective but has an antipruritic effect. Sulfur (3% to 6% in petrolatum or cetaphil lotion) is used primarily in pregnant women and young infants in whom lindane and permethrin are not safe.

Human contact with other species of scabies mite, such as *Sarcoptes scabiei* variant *canis*, the cause of canine sarcoptic mange, may cause pruritic papules where the mite bites, but the mite will not be able to burrow and set up an infestation similar to human scabies. Thus, treatment of the pet is essential, and a scabicide for the human friend is not indicated. Topical antipruritics and antihistamines will help control itching.

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Laser Therapy for Benign Pigmented Cutaneous Lesions

PIGMENTED EPIDERMAL LESIONS such as lentigines and café au lait macules present a therapeutic problem, as treatment is usually done for cosmetic benefit and may result in objectionable hypopigmentation, hyperpigmentation, epidermal atrophy, or scarring. Dermal pigmentation such as melasma, a nevus of Ota, blue nevi, and tattoos cannot be removed without scarring using current therapies.

Because of these problems, removal of these lesions with the use of lasers has been a consideration. The argon laser (wavelength 488 nm and 514 nm) is appropriate when melanin is the target, but its continuous output results in the delivery of too much thermal damage to the epidermis to be useful as selective therapy for pigmented lesions. This excessive energy causes heat damage and resultant slow wound healing with the potential of scarring.

The next laser to be used in the treatment of pigmented lesions was the carbon dioxide laser (wavelength 10,600 nm). Although this laser is not specific for pigment absorption (its target is any water-containing tissue), its advantage has been its extreme precision, especially when used in a superpulsed mode (a feature that minimizes unwanted thermal damage) and with low-energy fluences. Used within these boundaries, the carbon dioxide laser has proved to be an improvement over the existing methods. The use of the carbon dioxide laser in this manner, however, requires skill and experience; it cannot be used for dermal lesions without scarring. The same adverse reactions as with the argon laser may occur in the treatment of epidermal pigmented lesions, but the skillful use of this instrument in appropriate cases will diminish the risk.

As mentioned in an earlier epitome, the ruby laser (wavelength 694 nm, pulse 60 nanoseconds) has been approved for removing decorative tattoos. This laser has been remarkably successful in removing blue or black tattoo pigment and has a low risk of scarring. The laser light penetrates the dermis and interacts with the tattoo pigment granules. Some of the superficial pigment is eliminated through an epidermal crust that forms, but the deeper dermal pigment is broken down into smaller particles that can be carried away by phagocytes.* Because of its success with tattoos and the fact that its wavelength is absorbed by melanin, the ruby laser has also been used for removing both epidermal and dermal pigmented lesions, with a marked decrease in the incidence of adverse pigmentary or textural changes.

The copper vapor laser (wavelength 511 nm, pulse 20 nanoseconds) has received US Food and Drug Administration (FDA) approval for the treatment of pigmented lesions. Although its wavelength is excellent for melanin absorption, the train of 20 nanosecond pulses delivered at 10,000 to 15,000 pulses per second results in enough cumulative thermal energy to the epidermis that it is not pigment specific. This laser removes epidermal lesions by ablating the epidermis in a controlled manner and offers improvement over existing conventional nonlaser therapy.

The Candela pigment laser (wavelength 510 nm, pulse 300 nanoseconds) has received FDA approval for the treatment of pigmented lesions of the epidermis. Its wavelength is too short, however, to allow penetration into the dermis and limits treatment to epidermal lesions. This laser, as well as the ruby laser, causes selective damage of melanocytes only, sparing adjacent non-pigment-bearing keratinocytes. When a pigmented epidermal lesion is treated with this laser, abnormal melanocytes are destroyed, and, after the superficial epidermal wound heals, melanocytes from normal adjacent skin migrate to the area, resulting in normal repigmentation of the treated area.

An alexandrite laser (wavelength 755 nm, pulse 100 nanoseconds) is being tested now as a second component of this pigment laser system, designed to reach dermal pigment in the same way as the ruby laser. The pigment lasers and the ruby laser both show great potential for selectively destroying epidermal and dermal pigmented lesions without the problems of scarring and pigment alteration.

*For more information on the ruby laser, see the epitome, "Tattoo Removal Using the Ruby Laser," page 190.

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Diagnosis of Neurofibromatosis

NEUROFIBROMATOSIS, perhaps the most serious common genodermatosis, occurs in about 1 of every 3,000 to 4,000 live births. Many different forms of neurofibromatosis have been identified. Two seem best established clinically, and their genes have been localized: neurofibromatosis 1 (classic von Recklinghausen's disease) on chromosome 17 and neurofibromatosis 2 (central or bilateral acoustic neuroma) on chromosome 22. Proof that these two variants have different genes supports the insistence that the clinical subtypes should be carefully distinguished.

The gene for neurofibromatosis 1 has not only been mapped to the long arm of chromosome 17 but also partly deciphered and cloned. It is large and complicated, and its products appear to help control the cell cycle. Neurofibromatosis 1 is characterized by a high spontaneous mutation rate: about half the patients represent a new mutation and have no family history of the disorder. For those who have two or more family members with neurofibromatosis 1, a genetic diagnosis, including prenatal diagnosis, can be reached with a high degree of accuracy using linkage analysis. Direct gene probes are being developed but are rarely applicable today.

The cutaneous examination remains a crucial and cost-effective part of the diagnosis of neurofibromatosis 1. The National Institutes of Health diagnostic criteria include three skin findings: six or more café au lait macules more than 5 mm in greatest diameter in prepubertal patients and more than 15 mm in diameter in pubertal patients; two or more neurofibromas or one plexiform neurofibroma; and axillary or inguinal freckling.

A number of cautions must be applied in using these findings. Sometimes it is simply impossible to make an accurate clinical diagnosis in an infant whose parents are unaffected. It is better to be truthful about any uncertainty than to make an error. Experience with African-American, Hispanic, and Native-American patients suggests that both café

au lait spots and axillary freckling are more common and less diagnostic in these groups.

The presence of Lisch nodules (melanocytic hamartomas of the iris) is another criterion. This is the most common clinical feature of the disease in adults. If a person older than 21 years does not have Lisch nodules, the diagnosis is not neurofibromatosis 1. Furthermore, Lisch nodules occur only in this disease and not in any other variants or other diseases. The ophthalmologic slit-lamp examination is essential if a patient is suspected of having this disorder.

Mast cells are a prominent histologic feature of cutaneous neurofibromas. Mast cell factors may stimulate nerve growth, so treatment with ketotifen fumarate, a mast cell blocker, has been tried as a preventive measure. There has been at least one such patient whose intense pruritus was relieved with the use of ketotifen.

Parents and patients often ask about the long-term prognosis. A recent study showed three categories of disability: lifelong (12%) with mental retardation and orthopedic and cosmetic problems; treatable (16%) with endocrine tumors, hypertension, and benign central nervous system problems; and fatal (5%) with malignant tumors and central nervous system tumors.

There is hope for patients with neurofibromatosis 1 as preventive and interventional therapies are available for specific problems and a precise genetic diagnosis is potentially available to their siblings and offspring.

The Neurofibromatosis Foundation, 141 Fifth Ave, Suite 7-S, New York, NY 10010, is a good source of information and support.

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Alerts, Notices, and Case Reports

Treatment of Dyspareunia Following Medical Illness

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SEXUAL DYSFUNCTION may derive from physical, psychological, or social disorders. When a woman experiences a major medical crisis, impaired sexual function often ensues. Sexual complaints generally fall into four categories: inability to reach orgasm, dyspareunia (Table 1), failure of intromission, and a lack of arousal or desire. These can all be affected by a major medical illness. Gynecologic therapies often lead to feelings of diminished femininity. Gynecologic surgical treatment that results in a partial or complete loss of reproductive organs may cause psychological reactions that affect sexual performance and identity.[1,2] Grief and depression over lost reproductive potential are severe in young women. Genital disease also can lead to feelings of being tainted or soiled. Sometimes the disability caused by illness is seen as retribution for real or imagined sins and transgressions.

Any major illness that interrupts normal daily activities has the potential to alter sexual function. Systemic diseases and their therapies cause fatigue, pain, and disability. Sensation may be lost due to neurologic impairment, surgical procedures, or drug therapy. Metabolic disorders alter circulating hormone levels and thereby produce sexual dysfunction. Mutilating operations involving limbs, breasts, and genitals dramatically affect self-image. Persons with changes in body configuration may perceive themselves as greatly diminished and devalued as sexual beings.[3-5]

Acute, serious illness leaves patients with decreased energy and strength. Feelings of weakness, fragility, and vulnerability are inevitable. Patients also fear that sexual activity will precipitate further damage or that disease will be transmitted to the partner through physical contact. Studies show that persons usually resume sexual activity at the same time they return to work.[6] Patients and their partners, however, often view the diminished sexual interest and activity of the recuperative period as final. Although the literature has indicated the need for sexual counseling in severely ill persons, the topic is not routinely covered with gynecologic patients and is rarely discussed with patients with other medical disorders.[7]

When evaluating patients for sexual dysfunction after medical and surgical illness, anatomic and physical impairments must be carefully assessed. After physical limitations have been defined, attention should be focused on psychological factors. Therapists counsel the patients regarding which sexual activities they can realistically enjoy. A person's past experience, present level of physical function, and projected level of activity all need to be integrated into the therapeutic plan. The goal is to enhance the patient's sexual function even if defined deficits continue.

In the following report, we describe the differential diagnosis and workup for a complaint of dyspareunia after a chronic medical illness with gynecologic involvement.

Report of a Case

The patient, a 57-year-old married woman, complained of pain on intercourse for a year. The dyspareunia started after a four-year bout of enterovaginal and enterocutaneous fistulas following two operations for small bowel and colon resection to treat an episode of bowel obstruction. She was diagnosed as having probable inflammatory bowel disease. When she was seen, the only medical problems were recurrent urinary tract infections and dermatitis.

During the course of the patient's medical treatment, she had become dependent on her husband. The husband was always available, would help the patient change her colostomy, and was essential in the wound care regimen. The patient was in and out of the hospital for four years. Twice she came close to dying. The couple slowly decreased their social activities and focused on the overwhelming medical problems. Separate activities such as golf, bridge, stamp collecting, and socializing with friends stopped. The couple's sexual relations stopped soon after the initial enteritis developed. A year after recovery, the patient had immediate

TABLE 1.—*Causes of Dyspareunia*

Type of Dyspareunia	*Cause*
Intromission Failure	
Congenital abnormalities	Müllerian failure, agenesis, fusion defects, imperforate hymen, transverse septae, exposure to diethylstilbestrol in utero
Anatomic lesions	Vaginal masses or tumors, pelvic relaxation—cystocele, rectocele, prolapse
Painful Intromission or Superficial Dyspareunia	
Infection	*Candida* sp, *Gardnerella vaginalis*, herpesvirus, other
Lack of hormonal support	Menopause, amenorrhea due to low estrogen level, postpartum low estrogen level
Mechanical	Poor episiotomy repair, fistulae
Allergy	Medication, lubricant, contraceptives
Deep Dyspareunia	
Adhesive disease	Endometriosis, pelvic inflammatory disease—intrauterine device or sexually transmitted disease (STD)
Masses	Ovarian cysts (especially corpus luteum), myomata, or other tumors
Other organ system disorders	Urinary tract infection, gastrointestinal (irritable or inflammatory bowel)
Other Causes of Dyspareunia	
Fertility concerns	Fear of pregnancy, infertility
Fear of STD	
Vaginismus	
Previous rape or abuse	
Drugs	Ethyl alcohol, medication

(Leventhal JL, Taylor M, Sadock V: Treatment of dyspareunia following medical illness. West J Med 1992 Feb; 156:196-197)

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vaginal discomfort after attempted intercourse. She was reevaluated by her gynecologist to determine if the pain was associated with adhesions or remaining inflammation of the vagina. She had no pain on inspection or deep palpation and had no scarring or inflammation of the vagina or introitus. Despite recurrent urinary tract infections, there appeared to be no urethritis or urethral pain. The patient also saw her internist, who thought that sexual intercourse would not cause a recurrence of her fistulas or of her enteritis.

The patient had, in fact, feared that intercourse would cause the recurrence of a vaginal fistula. She felt that she was damaged "down there" and had a painful memory of her draining vaginal fistula. She also reported that her relationship with her husband had changed greatly. She complained that he would "hover" over her and that he was anxious about her health despite her year of recovered good health. He in turn reported that his wife had not resumed her social activities, that she was highly dependent on him, and seemed mildly reclusive and sad. She did not have a clinical depression, however.

Based on the history and medical workup, the patient was diagnosed as having a phobic reaction to intercourse with fears of a fistula recurring. She had difficulties with lubrication and arousal, as well as some introital spasm, which were due to anxiety about resuming sexual relations. Both the patient and her husband needed assurance that sexual intercourse would not result in physical damage or a recurrence of illness. The couple was started on a standard behavioral therapeutic approach with mutual body massage for a few weeks, followed by erotic massage, and then, eventually, intercourse. The couple was advised to approach intercourse gently initially and to use progressive desensitization for intromission. Following this approach, the patient gradually began lubricating normally and became aroused during the massage exercises. The introital spasm disappeared. The couple's interdependence was alleviated by assigning social activities. Also, the patient's dermatitis and recurrent urinary tract infections resolved. The couple chose to continue daily massage, as they found it relaxing.

Discussion

This couple suffered from a number of problems in their sexual functioning. Initial considerations included psychological factors in the relationship, dyspareunia due to surgical residua, urethritis, cystitis, and anxiety around a fear of vaginal damage. After a complete evaluation, it appeared that psychological factors in the relationship and an anxiety reaction to the patient's prolonged illness were the primary reasons for her dyspareunia. Anxiety, decreased functioning of the couple socially and sexually, and frustration of the husband largely resolved with a behavorial approach to their sexual problems and daily interactions. With a return to normal functioning, the couple recovered from the trauma inflicted by a life-threatening illness.

Others have reported on psychosexual reactions in patients with chronic bowel disease.[8-11] Resistance to evaluating sexual functioning in women who have undergone major medical illness may be due to inexperience on the part of therapists in the differential diagnosis of female sexual dysfunction, a lack of awareness of the frequency of sexual dysfunction following illness, or a fear that such history taking will "open a Pandora's box of problems." The critical factors in therapy are the previous level of sexual functioning, the previous state of sexual relations, and the cause of the present dysfunction. If previous functioning and sexual relations have been good, then the treatment focuses on the physical and the psychological contributions to the current problem. Sexual dysfunction following severe illness can often be treated successfully with a behavioral approach.

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Botulism Immune Globulin for Infant Botulism Arrives—One Year and a Gulf War Later

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ABOUT A YEAR AGO, we directed the WESTERN JOURNAL OF MEDICINE's readers to the clinical trial of botulism immune globulin (BIG), planned to start on January 1, 1991.[1] This clinical trial was intended to assess the efficacy of botulism immune globulin (a human "antitoxin"), supplied by the United States Army, in the treatment of infant botulism. Unfortunately, before the study could begin, the war in the Persian Gulf intervened, and the Army found it necessary to retain its supply for defense against biochemical warfare.[2]

Faced with a delay of unknown length, the California Department of Health Services, with US Food and Drug Administration (FDA) support, created a new supply of BIG. All steps, beginning with the collection of botulism immune plasma from previously immunized volunteer donors, were done in accord with FDA regulations and licensure requirements. Donated plasma was screened for antibody against the human immunodeficiency virus, hepatitis C, and human T-lymphotropic virus type I, in addition to other standard testing. The Massachusetts Public Health Biologic Laboratories, a facility licensed for the production of intravenous immune globulin, fractionated the immune plasma into BIG.

(Schwarz PJ, Arnon SS: Botulism immune globulin for infant botulism arrives—One year and a Gulf War later. West J Med 1991 Feb; 156:197-198)

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The new supply of BIG is expected to be available by February 1, 1992. The clinical trial will open formally for patient enrollment on that date. Botulism immune globulin should be administered as early in the course of infant botulism as possible to stop the progression of symptoms, which generally include constipation, weakness, ptosis, disconjugate gaze, weak cry, poor suck, diminished gag reflex, expressionless face, head lag, diffuse hypotonia, and, not infrequently, respiratory arrest. Physicians who suspect infant botulism may obtain BIG for their patients by calling the study office's 24-hour, 7-days-a-week telephone number: (510) 540-2646.

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Exacerbation of Motor Tic and Induction of New Tic by Haloperidol Use

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TIC DISORDERS may be classified as simple tics, chronic motor tics, or Tourette's syndrome.[1-3] Chronic motor tics occur early in childhood or before the age of 21 years. The severity and type of symptoms tend not to change over time, and chronic motor tics are usually limited to a single type of tic. The duration of the illness is lifelong. Chronic motor tics have specific diagnostic criteria,[1,3] but their prevalence is not known.[2] Therapy for chronic motor tics is rarely needed because the tic is usually not severe. Chronic motor tics should be differentiated from simple tics, which are the mildest of the tic disorders, lasting as long as a year.[1-3] Tourette's syndrome and chronic motor tics appear to be genetically related.[4-6] Haloperidol was first used in 1961 to treat Tourette's syndrome.[7] Case reports indicate that haloperidol therapy provides good to excellent control of tics.[1] A Tourette-like syndrome has been described as occurring as a result of the long-term use of neuroleptic drugs[8] and following low-dose short-term neuroleptic drug therapy[9] among patients with previously diagnosed neurologic or psychiatric disorder.

We report a case of chronic motor tics exacerbated by short-term treatment with haloperidol and the concomitant development of a new tic.

(Diaz JM, Smith KG, Maccario M: Exacerbation of motor tic and induction of new tic by haloperidol use. West J Med 1992 Feb; 156:198-199)

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, the Department of Defense, or the US Government.

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Report of a Case

The patient was a 19-year-old man in whom motor tics developed at 4 years of age. The tic consisted of a repetitive turning of the neck to the right side. This symptom was exacerbated by stress, anxiety, or strenuous physical activity. The patient reported only one type of tic and denied ever having vocal tics, coprolalia, palilalia, or echolalia. While on military duty in Korea, the stress of his overseas tour seemed to exacerbate his tic, which became more frequent and of greater amplitude. He was treated with haloperidol, 0.5 mg three times a day. A week after the treatment was started, the tic became even more frequent and a "new tic" developed. He described this new tic as stereotypic buccal movements without vocalizations or sounds. After 20 days of treatment, the haloperidol therapy was discontinued. The new tic disappeared, and the frequency and amplitude of the chronic tic returned to its initial state.

Discussion

Tourette's syndrome, as a genetic disorder, has been studied extensively.[4,6,10-12] Although chronic motor tics have been considered a different diagnostic disorder,[1,3] they have been genetically linked to Tourette's syndrome[4-6]; some reports question this possibility, however.[13] Tourette's syndrome can be exacerbated by central nervous system stimulants[14,15] and cocaine.[16] A Tourette-like syndrome has been described as occurring during the long-term use of neuroleptic agents, during drug withdrawal,[8] and with short-term neuroleptic drug therapy.[9] This Tourette-like syndrome is considered analogous to tardive dyskinesia associated with chronic neuroleptic drug therapy.[9] The pathophysiologic mechanism for the development of Tourette-like syndrome is thought to be a "chemical denervation supersensitivity of dopamine receptors following chronic neuroleptic blockade."[9,17]

In patients with Tourette's syndrome treated with haloperidol, acute dystonias, dyskinesias,[18] akathisias,[19] or an exacerbation of their tics can develop.[20] Karagianis and Nagpurkar reported the case of a 10-year-old boy in whom features of Tourette's syndrome developed while he was being treated with haloperidol for behavior problems.[21] His symptoms worsened as the haloperidol dose was decreased and improved as the dose was increased. In cases with an acute exacerbation or an initial onset of motor tics after

TABLE 1.—*Treatment Options for Tics and Tourette's Syndrome**

Drug†	*Dosage, mg at bedtime*	*Side Effects*
Haloperidol . .	0.5, to be increased every 5 d up to 10/d	Depression, sedation, dysphoria, weight gain, tardive dyskinesia, cognitive impairment, interference with motivation and learning, and exacerbation of tics
Pimozide	1, to be increased up to 10/d	Electrocardiographic changes —T-wave inversion, U waves, QT prolongation, and bradycardia—and mental depression
Clonidine	0.05, to be increased gradually to 0.15 to 0.30/d	Sedation, hypotension, and dizziness

*From Van Woert.[24]
†Other less effective medications are phenothiazines, tetrabenazine, and clonazepam.

neuroleptic drug therapy, the most probable mechanism is presynaptic dopamine blockade.[17] Tics can be induced by carbamazepine,[22] tricyclic antidepressants,[23] and central nervous system stimulants.[15] We were, however, unable to find a report in which treatment with haloperidol exacerbated chronic motor tics.

Our patient had two complications of neuroleptic drug use. He suffered an acute exacerbation of his chronic motor tic disorder and the occurrence of a new motor tic. We propose that the pathophysiologic mechanism for both conditions was mediated by presynaptic dopamine blockade. Symptoms of Tourette's disorder—tics, coprolalia, obsessive behaviors—have been found to worsen with haloperidol treatment.[20] Given the ample evidence associating chronic motor tics with Tourette's syndrome, it is logical to expect similar reactions to treatment with haloperidol. Haloperidol, however, has been shown to prevent the worsening of tics induced by central nervous system stimulants.[14] In our case, treatment with haloperidol exacerbated a preexisting motor tic and induced a new tic.

Given the possible complications associated with haloperidol treatment, there are several options available for the treatment of chronic motor tics and Tourette's syndrome (Table 1).[24] For most patients who have an exacerbation of motor tics or the development of Tourette-like syndrome after neuroleptic drug therapy, these will resolve with the discontinuation of the drug.[20] Treatment with an anticholinergic agent could be another available alternative. Physicians should know of the possible development of motor tics or exacerbation of preexisting motor tics during treatment with haloperidol. It is important to recognize them as neurologic rather than psychological manifestations[25] so they may be appropriately managed.

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Pursuing an Occult Carcinoma in a Patient With Subacute Cerebellar Degeneration and Anticerebellar Antibodies

Need for Vigorous Follow-up

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PARANEOPLASTIC CEREBELLAR degeneration is an uncommon complication of systemic malignancy. The disorder is characterized clinically by the rapid or subacute development of extreme ataxia, dysarthria, and nystagmus, producing a cerebellar deficit of almost unique severity.[1,2] Pathologic findings in affected patients include extensive, often complete loss of Purkinje cells, with variable loss of granule cells.[1,2] The disorder has been associated with a number of malignant neoplasms, including adenocarcinomas of the ovary, fallopian tube, uterus, and breast, small-cell carcinoma of the lung, and Hodgkin's disease.[1,2] Paraneoplastic cerebellar degeneration may develop as long as two or more years before the detection of a malignant tumor, during its course, or at a time when the carcinoma is thought to be in remission.[1-4]

(Greenlee JE, Brashear HR, Jaeckle KA, Geleris A, Jordan K: Pursuing an occult carcinoma in a patient with subacute cerebellar degeneration and anticerebellar antibodies—Need for vigorous follow-up. West J Med 1992 Feb; 156:199-202)

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomography
Ig = immunoglobulin
PBS = phosphate-buffered saline

The cause of paraneoplastic cerebellar degeneration is unknown. In recent years, however, antibodies reactive with cerebellar and other neurons have been repeatedly shown in serum and cerebrospinal fluid (CSF) of affected persons.[3-25] This antibody response is rarely, if ever, detected in the absence of neoplasia, and the presence of antineuronal antibodies in a patient with subacute cerebellar degeneration thus provides strong presumptive evidence of an underlying tumor.[3-17] In some antibody-positive patients presenting with cerebellar degeneration, however, a meticulous search may initially fail to identify the associated malignant disease. The case reported here emphasizes the need for vigorous, prolonged follow-up in antibody-positive patients in whom the search for an occult neoplasm is initially unsuccessful.

Report of a Case

The patient, a 52-year-old woman, was in good health until November 1985, when she awoke with diplopia on right lateral gaze and noted mild difficulty walking. A neurologic examination done the next day showed a left inferior rectus weakness, mild nystagmus on left lateral gaze, and diplopia that was most pronounced on right lateral gaze. No other abnormalities were detected. Over the next two weeks, diplopia on left lateral gaze developed, and she had progressive unsteadiness of gait and difficulty writing. When the neurologic examination was repeated, she was found to have ataxia. The results of hematologic studies, blood chemistry values, and serum protein electrophoresis were normal. A lumbar puncture revealed 68 × 10^6 per liter leukocytes (0.98 lymphocytes), a protein level of 0.67 grams per liter (67 mg per dl), and a glucose value of 3.4 mmol per liter (61 mg per dl) (Table 1). Two oligoclonal bands were present, and the CSF immunoglobulin (Ig) G synthesis rate was increased to 19.8 mg per hour (normal < 3.5 mg per hour). Cytologic examination of CSF did not reveal malignant cells, and cryptococcal antigen was not detected. Visual-evoked response tests, computed tomography (CT), and magnetic resonance imaging of the head with gadolinium enhancement were normal. The results of subsequent CSF examinations are shown in Table 1. Cultures of CSF were negative for bacteria, acid-fast bacilli, and fungi, as were serologic studies for *Toxoplasma gondii, Mycoplasma pneumoniae, Coccidioides immitis,* and several viral agents including herpes simplex virus, Epstein-Barr virus, and human immunodeficiency virus. An extensive search for an occult carcinoma, including pelvic and abdominal ultrasonography, mammography, chest CT, bronchoscopy, upper gastrointestinal series, and barium enema, elicited no abnormalities.

Over the next month, the patient's speech, gait, and coordination continued to deteriorate. A neurologic examination in January 1986 revealed skew deviation with diplopia and nystagmus in all directions of gaze. Speech was dysarthric. Strength was normal, but the patient had a prominent perpendicular tremor on finger-to-nose and heel-to-shin testing, as well as severe truncal ataxia. The patient was able to stand with support but was unable to walk. An electroencephalogram revealed mild left temporal slowing. Head CT was normal. A serum assay for anticerebellar antibodies produced type I ("anti-Yo") staining typical of that produced by serum from patients with paraneoplastic cerebellar degeneration associated with ovarian and breast carcinomas (Figure 1). The results of breast examinations and mammography were negative, however, and pelvic examination under anesthesia and laparoscopy disclosed a normal uterus, normal adnexa, and atrophic ovaries. Treatment with prednisone and azathioprine failed to halt the progression of the patient's cerebellar deficit, as did six courses of plasmapheresis. The patient subsequently underwent laparotomy and bilateral oophorectomy, without detection of malignancy. She remained neurologically stable over the next 21 months, with prominent nystagmus in all directions of gaze, severe dysarthria with scanning speech, and profound truncal and appendicular ataxia. No evidence of tumor was found during follow-up visits. On December 7, 1987, however, repeat mammography detected a 1.5-cm lesion in the upper outer quadrant of the right breast, and needle biopsy revealed an infiltrating mammary carcinoma. The patient was treated with mastectomy and local radiotherapy. The patient has remained neurologically stable, with persisting profound neurologic deficit.

Materials and Methods

The assay for anticerebellar antibodies in serum and CSF was done as previously described.[4] Serial twofold dilutions of serum beginning at a dilution of 1:20 and of CSF beginning with undiluted material, prepared in phosphate-buffered saline solution, were reacted with sections of autopsy human cerebellum for 60 minutes at 37°C. Sections were washed in phosphate-buffered saline solution, reacted with a 1:20 dilution of fluorescein isothiocyanate-conjugated rabbit anti-human IgG, washed, coverslipped, and examined using

TABLE 1.—*Cerebrospinal Fluid (CSF) Findings and Anticerebellar Antibody Titers During Onset and Progression of Paraneoplastic Cerebellar Degeneration*

Date	Cells × 10^6/liter	Lymphocytes*	Glucose, mmol/liter (mg/dl)	Protein, grams/liter (mg/dl)	Anticerebellar Antibodies	
					Serum Titer	CSF Titer
11/27/85	0.68	0.98	3.4 (61)	0.67 (67)	N/A	N/A
12/03/85	0.47	0.95	3.2 (58)	0.52 (52)	N/A	1:320
1/07/86	0.16	1.00	3.8 (69)	0.15 (15)	1:2,560	1:20
3/10/86	--	†	--	--	1:320b‡	N/A
2/22/89	--	†	--	--	1:640	N/A

N/A = not assayed

*Values represent a fraction of 1. †A CSF specimen was not obtained. ‡Following plasma exchange.

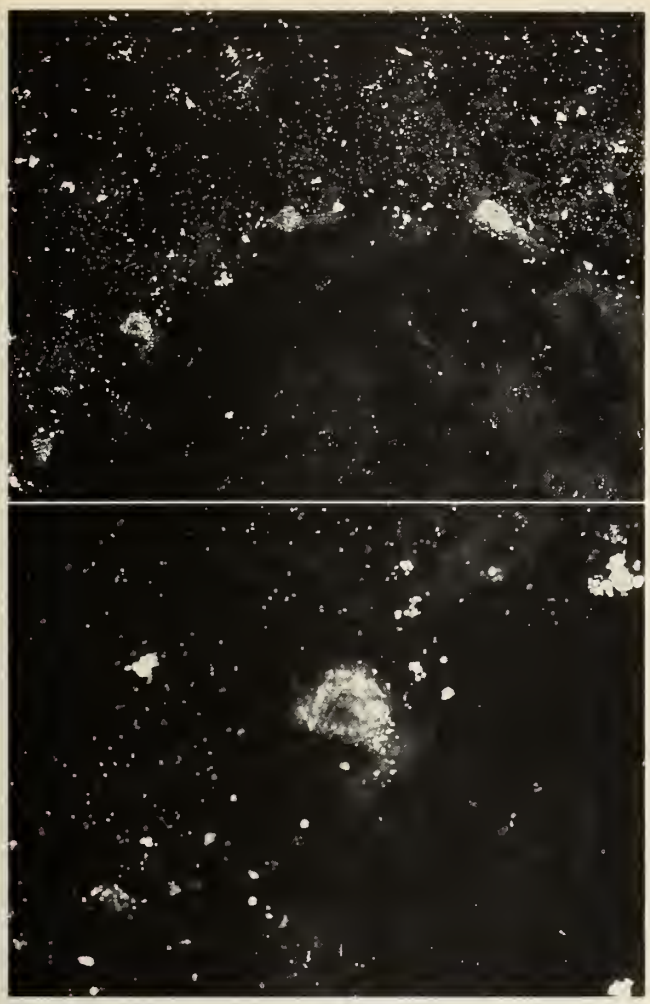

Figure 1.—**Top,** A section of normal human cerebellum overlaid with a 1:40 dilution of the patient's serum and stained using indirect immunofluorescence methods shows intense staining of Purkinje cells. The punctate extracellular fluorescence seen in this section is due to lipofuchsin (original magnification × 150). **Bottom,** A Purkinje cell labeled with the patient's serum at a dilution of 1:40 and stained using indirect immunofluorescence methods shows intense granular cytoplasmic staining of the cytoplasm with sparing of the cell nucleus (original magnification × 625).

a Leitz Ortholux microscope with a 495-nm excitation filter and a K530 barrier filter. Controls consisted of matched sections of cerebellum reacted with known positive and negative serum. All studies were carried out with Institutional Review Board approval and with appropriate informed consent.

Results

A serum specimen obtained on January 7, 1986, and submitted for assay for anticerebellar antibodies produced bright, coarsely granular cytoplasmic staining restricted to cerebellar Purkinje cells through a dilution of 1:2,560 (Figure 1 and Table 1). A CSF specimen obtained concurrently produced an identical pattern of immunofluorescence staining through a dilution of 1:20. Testing of a specimen of CSF from the patient's December 3, 1985, lumbar puncture was positive through a dilution of 1:320. A serum specimen obtained on March 10, 1986, after the patient's final plasma exchange, produced staining through a dilution of 1:320. A serum titer on February 22, 1989, after detection and treatment of the patient's tumor, was 1:640.

Discussion

Two major patterns of antibody response have been associated with paraneoplastic cerebellar degeneration. Serum from patients with paraneoplastic cerebellar degeneration accompanying adenocarcinomas of the ovary, uterine adnexa, uterus, or breast contains antibodies that recognize a cytoplasmic antigen restricted to cerebellar Purkinje cells, deep cerebellar nuclei, and certain brain-stem nuclei.[3-5,8,10,15] Immunoblot studies have shown that this antibody response, called type I or anti-Yo, is directed against proteins with molecular weights of 37 and 62 kilodaltons (kd).[3,18] Type I antibody response has not been associated with paraneoplastic syndromes other than cerebellar degeneration.[3-5,8,10,11,15,17] In contrast, serum and CSF from patients with paraneoplastic neurologic syndromes associated with small-cell carcinoma of the lung contain antibodies that produce intense nuclear labeling and varying degrees of homogeneous cytoplasmic staining of virtually all neurons.[6,8,9,16] This antibody response has been called type II or "anti-Hu." Immunoblot studies have shown that type II antibodies recognize a group of proteins whose molecular weights range from 35 to 40 kd.[9] Type II antibody has been associated with various paraneoplastic neurologic syndromes, including cerebellar degeneration, limbic encephalitis, brain-stem encephalitis, and dorsal sensory neuronopathy.[6,9,16] An antibody producing a similar pattern of immunostaining ("anti-Ri") but reacting with 53 to 61 and 79 to 84 kd antigens has been described in patients in whom paraneoplastic opsoclonus develops in association with carcinoma of the breast.[19,20] Antibodies producing other patterns of immunohistologic staining and recognizing other protein in immunoblots have been described in a minority of patients with paraneoplastic cerebellar degeneration.[7,13,14,21] In each instance, the antibodies have been specific for neurons and have not labeled normal extraneural tissue. Type I antibodies have been shown to recognize cellular antigens within the patients' tumors, suggesting that the antibody response in paraneoplastic cerebellar degeneration and other paraneoplastic neurologic syndromes may be elicited by tumor antigens that are immunologically similar to neuronal proteins.[22] Although antibodies have repeatedly been detected in the CSF of affected patients, a spontaneous fall in CSF antibody titers during disease progression, as occurred in this patient, has not been reported previously.

Experience with antineuronal antibodies as markers for occult malignancy is still limited. Types I and II antibody responses are strongly associated with cancer, however. Gynecologic or breast cancers have been identified in all but three patients thus far reported in whom type I antibody has been detected.[17] One of these three patients was found to have a lymphoma, but it was not thought that a gynecologic tumor had been excluded.[17] The other two patients are still being observed.[17] Hetzel and co-workers have recently reported the cases of seven patients with progressive cerebellar deficits in whom the detection of a type I serum antibody response led to the diagnosis of ovarian adenocarcinoma.[15] Type II antibody, as confirmed by immunohistologic and immunoblot studies, has been reported almost exclusively in patients with small-cell carcinoma of the lung.[3,6,8,9,16] These data suggest that anticerebellar antibodies should be sought as part of a thorough neurologic evaluation in any adult patient with a rapidly progressive cerebellar deficit.

In the present study, a patient with subacute cerebellar degeneration was found to have serum and CSF antibodies that produced immunofluorescence staining of cytoplasmic antigens of cerebellar Purkinje cells, characteristic of type I antibody response. Because the results of a breast examination and mammography were unremarkable, extensive search was undertaken for a pelvic malignant neoplasm. Efforts to detect a tumor culminated, as the patient's clinical condition continued to worsen, in exploratory laparotomy and bilateral oophorectomy. Despite this exhaustive search, the associated tumor, a breast carcinoma, was not detected until more than two years after the onset of the patient's cerebellar deficit. Type I antibody is most frequently associated with gynecologic malignancy, and its reported use as a predictor of occult malignancy has been restricted to carcinoma of the ovary, uterus, and adnexa.[15] An identical antibody response may occur in patients with carcinoma of the breast, however.[3,5] Meticulous follow-up with careful search for an occult tumor should thus be continued in antibody-positive patients in whom a tumor is not found. The possibility of breast as opposed to ovarian, uterine, or adnexal adenocarcinoma should be kept in mind in any patient with type I antibody response. Repeat mammography, in addition to further careful gynecologic evaluation, should be considered in any patient in whom type I antibody is detected but a neoplasm not initially found, with repeat evaluations at three- to six-month intervals over the next year or two.

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The Papanicolaou Smear

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EVIDENCE IS overwhelming that cytologic screening has been instrumental in effecting a reduction of both incidence and mortality rates of invasive cervical carcinoma.[1-9] The death rate from cervical cancer has decreased by 50% to 70% since the Papanicolaou smear was introduced. Papanicolaou smears are convenient, painless, sensitive, cost-effective, quick, and widely accepted. They are an important part of good care of patients and can help avoid litigation for failure to diagnose cervical cancer.

Limitations of Papanicolaou Smears

Papanicolaou smears are only a portion of a complete pelvic examination. Cervical cytology as a screening test has an incidence of both false-negative and false-positive results.[10-25] These problems will vary with collection technique, the laboratory involved, and patient demographics. Because cervical cytology is a screening test, abnormal findings have to be confirmed histologically.

Suspicious cervical lesions should be evaluated regardless of cytopathologic findings. A biopsy should be taken of gross lesions. Colposcopically directed biopsies are indicated for accurate localization of optimum biopsy sites if an

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obvious lesion is not visible. Doing random cervical biopsies is discouraged. If cytopathologic, colposcopic, and histopathologic findings do not correlate, additional evaluation is indicated.

Techniques for Specimen Collecting

Scraping the transformation zone is the most important step in collecting a Papanicolaou smear. The cervix should be scraped firmly, but care should be taken not to cause bleeding. Slides should not be made too thick. An endocervical specimen is important,[26,27] preferably one obtained by the use of a brush[28,29]; however, a saline-moistened cotton applicator or a "sword" is acceptable.

Careful attention to technique can reduce the incidence of unsatisfactory smears and thus reduce the occurrence of false-negative tests.[25] Less than optimum smears are often the result of the following:

- A thick smear with an abundance of red blood cells or inflammatory cells,
- Poor fixation, often caused by air drying,
- A scarcity of cells caused by wiping the cervix before obtaining the smear specimen,
- Inadequate scraping,
- An absence of endocervical cells,
- Failure to obtain an endocervical specimen.

Inadequate fixation is a problem. Specimens should not be allowed to air dry, so speed is important. Any fixation method used should be approved by the pathologist reading the slide. Thus, communication between clinician and pathologist is important.

Adequacy of Papanicolaou Smear Specimens

The midportion of the menstrual cycle is the optimal time to take a Papanicolaou smear; smears obtained at other times of the cycle, however, are much better than none at all.[25] A menstrual smear is not necessarily an unsatisfactory smear.

A virtually acellular smear is unacceptable and must be repeated. The presence of blood or inflammation affects accuracy. The amount permitted varies with each laboratory. The laboratory *must* report the presence or absence of endocervical cells because the absence of such cells makes uncertain the adequacy of the test.[26]

One slide is considered satisfactory, but two slides are acceptable. Vaginal pool specimens are considered by most to be of limited usefulness.

Reports

Verbal communication between the clinician and pathologist is important. There is no objection to using a Papanicolaou classification system by numbers, but a report is inadequate if no verbal description is given.[30,31]

The degree of inflammation should be reported. Because evaluations will vary from laboratory to laboratory, the clinician must communicate with the pathologist. The treatment of obvious vaginal infection before a smear is done is optimal; a smear must be made if there is any question regarding patient compliance.

A smear should be repeated soon if it is inadequate because of inflammation. If the smear is adequate but there is any inflammation or other benign atypia, it should be repeated in three to six months. Colposcopy is recommended if there are two abnormal smears with benign atypia or inflammation not accounted for by the presence of a specific etiologic agent.

The presence of koilocytes is diagnostic for human papillomavirus infection of the cervix. The cells are characterized by sharply defined perinuclear cavitation bordered by dense, amphophilic cytoplasm. Nuclei show hyperchromasia and may be multiple. Both nuclear changes and perinuclear cavitation must be present.

The presence of endometrial cells should be reported regardless of the age of the patient. Any unusual finding should likewise be reported. As indicated earlier, communication regarding unusual findings is important.

Evaluation of Laboratories

Physicians should consider the following questions before selecting a cytology laboratory[25,32,33]:

- Is the laboratory licensed by the College of American Pathologists? Is it accredited by a volunteer accrediting agency?
- Is there good communication between the cytology laboratory and referring physicians? Does the location of the laboratory encourage such communication? When any new or unsuspected abnormality is found, the physician should be contacted, usually by phone.
- Does the laboratory report unsatisfactory specimens when, for example, there are too few cells for a valid interpretation? The percentage of unsatisfactory specimens will vary with the quality of the submitted specimen.
- Is there documentation of a quality assurance program in the cytology laboratory? Such documentation is required for American College of Pathologists accreditation; thus, an accredited laboratory has a quality assurance program.
- Are adequate staff available to do the work of that laboratory? Are certified cytotechnologists doing the work?

The Human Papillomavirus Epidemic

The human papillomavirus is a factor in the development of carcinoma of the cervix.[34-38] The herpes simplex virus type 2[38] or smoking[39] may likewise be associated.

The prevalence of the human papillomavirus infection varies widely among different population groups. This infection is the most rapidly increasing sexually transmitted disease in this country. Its prevalence is especially high in young adults. Regardless of a person's age, cervical cytologic screening should start when sexual activity begins. The epidemic will get worse before it gets better.

Although 60 types of the human papillomavirus have been identified, not all are related to cancer. Types 16, 18, 31, 33, and 35, among others, have been implicated in both squamous cell carcinoma and adenocarcinoma of the cervix.

A substantial lag time exists between what is seen in women and what is seen in men. Specimens from the sexual partners of female patients with the human papillomavirus infection should be examined using magnification and appropriate staining techniques. Accurate localization of optimum biopsy sites is indicated.

There is concern that characteristics of cervical cancer may be changing, with some lesions progressing rapidly.[40] This is possibly related to the type of associated human papillomavirus. There is evidence that the prognosis is influenced by the human papillomavirus type.[40]

Guidelines

Papanicolaou smears should be done annually after a woman becomes sexually active or reaches the age of 18 years.[41-43] There is no age limit above which annual Papanicolaou smears are not recommended.[23,41] The following reasons are given for these recommendations:

- The annual physical examination has proved a crucial, highly effective preventive measure.
- The increased diagnostic yield of annual Papanicolaou smear screening is cost-effective because everyone needs an examination anyway.
- The Papanicolaou smear is an easy, inexpensive, and painless test to do.
- The human papillomavirus epidemic is a problem of enormous magnitude.
- The screening frequency compensates for a lack of patient compliance.
- Annual screening should increase persons' compliance in other areas of health care screening.

High-risk persons may require screening more often than annually. These include women who began their sexual activity early, women with multiple sexual partners, patients with a history of any lower genital tract infection of any disease related to the human papillomavirus, those with sexual partners who have had any disease related to the human papillomavirus, and women who had exposure to diethylstilbestrol in utero.

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Editorials

The Complex Relation Between Tubular Injury and the Glomerular Response in Acute Renal Failure

OUR VIEW OF the pathogenesis of acute tubular necrosis has been greatly conditioned by results derived from experimental models of acute renal failure in animals. Studies in animals originally focused on the specific mechanisms causing the major reduction in glomerular filtration rate (GFR): renal vasoconstriction, tubular obstruction, transepithelial backleak of filtrate, and reduction in the glomerular ultrafiltration coefficient. More recent experimental studies have focused on causes of tubular injury and mechanisms of protection. As Stein has observed elsewhere in this issue,[1] the four mechanisms contributing to reductions in GFR with acute tubular necrosis can readily be segregated into glomerular mechanisms (that is, renal vasoconstriction and decreased glomerular ultrafiltration coefficient) and tubular mechanisms—obstruction and backleak. Based on experimental studies in animals[2-4] and the unique observations of Myers and coworkers,[5,6] only 25% to 50% of the reduction in whole kidney-GFR in acute tubular necrosis can be attributed to glomerular mechanisms—renal vasoconstriction and reductions in the glomerular ultrafiltration coefficient—with the remaining 50% to 75% being caused by tubular backleak and obstruction. Even these estimates of the relative contributions of glomerular and tubular factors to the reduction in GFR are temporally dependent, with glomerular factors assuming importance early in the process of acute renal failure[3] and tubular obstruction making greater contributions to GFR reduction with time,[2,7] as suggested by Stein in his article.

The separation of glomerular and tubular contributions to the reduction in GFR is partially artificial because there is a strong interaction between tubular injury and reductions in nephron filtration rate at glomeruli. Tubular obstruction due to cellular debris and casts may simply affect glomerular ultrafiltration by elevating tubular pressure, thereby decreasing the glomerular capillary hydrostatic pressure gradient (ΔP). Stein has pointed to the study of Arendshorst and associates,[8] in which they observed that tubular obstruction with time contributes to renal vasoconstriction—reductions in glomerular capillary hydrostatic pressure and nephron plasma flow—resulting in a normal tubular pressure. The specific mechanisms whereby tubular obstruction communicates to the vasomotor elements at glomeruli are not known but may involve long-term adaptation of the macula densa–tubuloglomerular feedback system.[9]

Studies of acute renal failure in animals have revealed other mechanisms by which tubular injury influences ultrafiltration at glomeruli. In models of nephrotoxic acute renal failure in which uranyl nitrate is administered, tubular obstruction is not an early finding, but the nephron filtration rate decreases.[4] We have observed that the administration of 0.5 ng of uranyl nitrate into the early proximal tubular lumen of single nephrons produces modest reductions in proximal tubular reabsorption and nephron filtration rate within 5 minutes, a period that precedes any evidence of transepithelial backleak of solutes.[3] The glomerular responses were associated with increases in early distal tubular sodium and chloride concentration. The 20% to 30% reduction in single-nephron GFR was totally prevented by concurrent intratubular perfusion with either 10^{-4} mol per liter of furosemide or 10^{-5} mol per liter of bumetanide.[3] These results strongly suggest that a component of the early reduction in the single-nephron GFR in certain forms of acute renal failure results from tubular injury, reductions in proximal tubular reabsorption, and the consequent activation of macula densa–tubuloglomerular feedback mechanisms, the normal physiologic mediator of the relation between tubular reabsorption and the nephron filtration rate.

Although activation of tubuloglomerular feedback mechanisms does not constitute the major contribution to a reduced GFR in acute renal failure, the contribution of this volume conservation system should not be underestimated. The activation of tubuloglomerular feedback and a reduction in the single-nephron GFR may enhance the likelihood of tubular obstruction with cellular debris due to further reductions in tubular flow rate. There is little direct evidence for a significant role for tubuloglomerular feedback activation in models of ischemic acute renal failure. Activation of these feedback mechanisms prevents the external fluid losses that might be a consequence of tubular injury and may also reduce the likelihood of continuing tubular damage. Therefore, the tubuloglomerular feedback–mediated reductions in single-nephron GFR after tubular injury could be considered beneficial to an organism from several mechanistic viewpoints.

The major goal of clinical and experimental studies of acute renal failure should be to develop useful therapeutic interventions. Stein has correctly pointed out that such therapeutic interventions must be conditioned by knowledge of the temporal evolution of acute tubular necrosis, derived primarily from experimental models in animals.[1] But what is the goal of therapeutic intervention: an immediate improvement in kidney GFR or a reduction of the degree of further tubular injury? These goals cannot be satisfied concurrently in all clinical conditions. Experimental models of acute renal failure have clearly suggested that maneuvers to prevent or ameliorate acute renal failure, such as previous volume expansion and possibly using certain diuretics, are correlated with increased osmolar clearance. Such a correlation could be the result of increased tubular flow rates with decreased likelihood of tubular obstruction, altered intrarenal hormonal status, or reductions in tubular reabsorption and O_2 and metabolic requirements. After several decades of discussion and investigation, the role of diuretic use in various stages of acute tubular necrosis is still largely unknown, and the issue remains confusing. Although volume expansion has been shown to be beneficial, possibly by means of the first two mechanisms mentioned earlier, in vivo experimental studies have not consistently shown benefit from diuretic administration in all forms of acute renal failure.

Recent studies have suggested that the administration of furosemide may ameliorate tubular necrosis, primarily in the thick ascending limb, in a model of ischemia in isolated perfused kidneys.[10] Furosemide provides benefit by decreasing tubular reabsorption and cellular metabolic demands in the thick ascending limb, thereby conferring relative resistance to profound ischemia. We have also observed in vivo that administering benzolamide, a carbonic anhydrase inhibitor acting primarily in the proximal tubule, immediately

after an hour of renal ischemia and throughout 24 hours of reflow resulted in the maintenance of proximal tubule integrity and improved proximal reabsorption and nephron filtration rate (unpublished observations). These results were likely the consequence of reductions in proximal tubular metabolic demands or "tubular work," but they may have also derived from greater osmolar clearance and tubular flow rates resulting in lesser degrees of tubular obstruction. There is a cogent logic to the application of diuretic agents that inhibit proximal tubular reabsorption under clinical conditions in which renal ischemia is likely, since the proximal tubule is an early site of ischemic damage in vivo.

Reductions in tubular reabsorption and decreases in the metabolic demands of tubular epithelia may diminish the degree of tubular injury in experimental acute renal failure; what, then, should be the consequences of increasing the GFR early in the course of incipient acute tubular necrosis? This is not a straightforward question to answer. Because GFR is highly dependent on renal blood flow, its improvement by pharmacologic intervention should improve blood flow and oxygen and substrate delivery to renal cells, a potentially beneficial effect. In addition, a higher GFR early in this process should increase the tubular flow rate and could diminish the tendency for tubular obstruction. Although this scenario would imply that an improvement in the GFR soon after tubular injury should prevent or ameliorate acute tubular necrosis, some studies suggest that early improvements in the GFR after tubular injury might produce adverse effects. Continuing tubular structural damage may be a consequence of a balance between the magnitude of the tubular insult, either ischemic or toxic, and the concurrent metabolic demands. The use of oxygen and substrate by the kidney is strictly linked to sodium chloride and sodium bicarbonate reabsorption. Improvements in renal blood flow and GFR lead directly to enhanced tubular reabsorption through glomerulotubular balance. Therefore, higher renal blood flow rate and GFR obligate greater tubular work, increasing the risk of tubular injury.

Recent studies from our laboratory have provided evidence for this phenomenon. We observed that pretreatment with the antioxidant probucol in a model of one-hour renal ischemia led to an increase in the nephron filtration rate two hours after reflow.[7] At 24 hours after reflow, however, proximal tubular damage and the impairment of proximal reabsorption were greater in probucol-treated rats.[2] The best explanation for these findings was that increases in the single-nephron GFR after tubular injury placed greater reabsorption-linked metabolic demands on injured tubules, leading to greater tubular necrosis (and prolonged duration of acute renal failure). Acute tubular necrosis represents a complex balance of glomerular and tubular events that act in concert to produce the clinical syndrome of acute renal failure.

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Why Is Cardiac Rehabilitation Not Widely Used?

THE REVIEW OF cardiac rehabilitation elsewhere in this issue clearly outlines the development of cardiac rehabilitative services and their current and future applications.[1] Gattiker and co-workers rightly focus on the goals, indications, and rationale for cardiac rehabilitative services, with an emphasis on exercise training; modification of coronary risk factors, especially hypercholesterolemia and smoking; behavioral treatments; education and counseling; and vocational rehabilitation. The review reflects, however, a major disconnection between what *ought* to be done in cardiac rehabilitation in an ideal world and what *is* done or *could* be done in a world of limited resources.

Rehabilitative and preventive services are generally underprovided in a medical care system that is primarily oriented to providing care for acute illness. The primary focus of cardiac rehabilitation is exercise training, which is generally given in a group setting. Risk factor modification is often provided by cardiac rehabilitation programs as well, but generally in a less well-developed and integrated way. The nearly 2,000 American cardiac rehabilitation programs are prized by patients for the supportive environment, peer support, and access to medical information that they provide. These programs offer many unique services that are lacking in the increasingly time-pressured acute care setting. Risk factors for coronary heart disease may indeed be more effectively managed through cardiac rehabilitation programs than through the usual channels of care. The current model of cardiac rehabilitation suffers from the following shortcomings:

- *Difficulty in distinguishing the effects of cardiac rehabilitation from those of physicians' usual care.* Effective therapies, including the use of thrombolytic and adjunctive drugs (antiplatelet, anticoagulant, and β-blocking agents) at the onset of acute myocardial infarction and mechanical revascularization (balloon angioplasty and coronary artery surgery) provided days or weeks later have not only reduced mortality but have improved the prognosis, enhanced functional capacity, and maximized occupational work potential. The success of these therapies has, or should have, shifted the focus of cardiac rehabilitation from exercise training to coronary risk factor management. Whether participating in cardiac rehabilitation programs substantially enhances the overall level of function of patients compared with usual care is not clear.

• *Lack of support by physicians.* Physicians may perceive that advice provided by cardiac rehabilitation programs regarding smoking cessation and hypercholesterolemia is duplicative or conflicts with their own. They are also often unfamiliar with methods for exercise training and skeptical that exercise improves the prognosis. Both of these factors have tended to limit physicians' willingness to refer their patients to cardiac rehabilitation programs.

• *Inconvenience of the group format.* Given a choice, many, if not most, patients prefer home-based to group-based exercise training because of the greater convenience of the former. Indeed, dropout rates from group programs at six months approach 50%. The proportion of patients classified as low risk and possibly eligible for home-based exercise training after an acute myocardial infarction has been substantially increased by the provision of effective therapy at the very start of an acute myocardial infarction.

• *Relatively low participation rates among eligible patients.* Fewer than 15% of patients undergo cardiac rehabilitation for a number of reasons. There may be logistical obstacles, especially the inconvenience of attending several class sessions for activities such as exercise training, which can be safely carried out by most patients at home. In one study, patients undergoing group-based training spent more time in their cars going to and from the program than patients in the home training program spent on their exercise cycles.[2] Moreover, many patients live a considerable distance from cardiac rehabilitation programs. Patients may not perceive any medical benefit of cardiac rehabilitation, especially those who are in a low-risk category. This diminishes their willingness to devote time and money to it. Insurance may not cover cardiac rehabilitation programs. Even if insurance reimbursement were not an issue, however, it seems unlikely that the proportion of patients participating in cardiac rehabilitation programs would more than double—that is, from 15% to 30%.

In fact, in recent years there has been a relative decline in the need for exercise rehabilitation after a myocardial infarction. There are several reasons for this that will be commented on briefly.

In the contemporary era of thrombolysis, exercise training does not measurably enhance the prognosis of patients after a myocardial infarction. Equally effective therapy, such as the use of β-blocking drugs, is much more convenient than exercise training and, unlike exercise training, is covered in the cost of usual care. More effective therapies, such as thrombolytic agents and adjunctive medical therapy provided at the start of an infarction, have dramatically decreased not only in-hospital but after-hospital mortality, which diminishes the potential of exercise training to lower mortality still further.

In the randomized Thrombolysis in Myocardial Infarction trial, phase IIB, in which patients receiving thrombolysis for myocardial infarction were randomly assigned to routine or elective balloon angioplasty, the total first-year mortality in both groups at one year was 7%: 5% through the 6th week and 2% through the 52nd week.[3] In contrast, in a study of cardiac rehabilitation conducted in the mid-1970s, the first-year after-hospital mortality alone was 15% among patients receiving usual care and significantly less—10%—among those undergoing exercise training.[4] In-hospital mortality in that era approximated 10% to 15%. It is clear that dramatic progress has recently been made in reducing the mortality of patients with acute myocardial infarction.

Of the studies of cardiac rehabilitation carried out in the 1970s, only that cited provides an accurate picture of prognosis after myocardial infarction because only this study randomly selected a consecutive series of patients soon—that is, 14 days—after the event.[4] This is in marked contrast to other exercise rehabilitation studies of that era in which the mortality in the year after enrollment was generally 3% to 5%. Indeed, many patients were enrolled as long as three years after a myocardial infarction. Because the death rate is highest during the first six months after such an event, late enrollment equates with low risk. Demonstrating the efficacy of *any* intervention is difficult in low-risk patients.

Today, with optimal thrombolytic and adjunctive medical therapy and mechanical revascularization starting at the onset of myocardial infarction, the first-year mortality is so low that many thousands of patients would be required to demonstrate the prognostic value of exercise training. The same is true of any therapy provided days or weeks rather than hours after myocardial infarction. Moreover, patients receive "bundled" medical therapy, including β-blocking, antiplatelet, and anticoagulant agents, that also contributes to a reduction in mortality.

In the contemporary era of thrombolysis, exercise training also exerts less effect on functional capacity. Thrombolysis, adjunctive medical therapies, and revascularization, which decrease early and late mortality, also preserve functional capacity. This reflects the extent of underlying left ventricular dysfunction and myocardial ischemia. A good prognosis, therefore, is tantamount to a well-preserved functional capacity, especially when the brief duration of contemporary hospital admissions for myocardial infarction minimizes physical deconditioning. Even before the thrombolytic era, the 50% of patients who were at low risk for subsequent cardiac events had a substantial spontaneous increase in functional capacity during the first three months after myocardial infarction.[5]

Exercise training designed to facilitate weight management and enhance psychological status and physical endurance can be provided in a home setting to a number of patients recovering from myocardial infarction. For example, exercise training can be safely carried out at home for most of the 50% of patients without significant left ventricular dysfunction or exercise-induced myocardial ischemia, whose risk is low. For the 30% of patients with exercise-induced myocardial ischemia whose risk for subsequent cardiac events has been diminished by revascularization, home exercise training can be safely carried out beginning four to five weeks after coronary artery operation or within two weeks after balloon angioplasty. For the 20% of patients with isolated left ventricular dysfunction, low-level home-based exercise training at an intensity approximating brisk walking can usually be carried out safely. Even relatively low-intensity exercise training continued over a six-month period enhances functional capacity. The risk of training-induced cardiac arrest is closely related to the intensity of exercise training. Reducing the intensity of exercise training is an important safeguard, therefore, especially when exercise training is home-based.

In the contemporary era of thrombolysis, exercise training does not significantly enhance the occupational work potential (as opposed to the functional capacity) of patients who have had a myocardial infarction, for the following rea-

sons. In the contemporary job market, the prognosis is much more important than functional capacity in determining occupational work potential. If the prognosis is good, functional capacity is generally well preserved.[6] In any event, there is little evidence that "work hardening"—exercise conditioning—is a prerequisite for return to work after a myocardial infarction, even for "blue collar" workers. Furthermore, functional capacity has declined markedly as a determinant of employability after such an event. Automation and mechanization have eliminated many jobs requiring heavy physical effort. Demographic shifts have further reduced the number of patients with ischemic heart disease whose jobs involve heavy physical work. The rate of retirement from the work force at age 62 is high even among patients without ischemic heart disease; young workers have supplanted older ones in performing the few remaining jobs that are physically taxing. Older workers whose prognosis is good—that is, those who do not manifest exercise-induced myocardial ischemia or left ventricular dysfunction—can continue to do heavy work. There is little evidence that subsequent cardiac events are more frequent among patients performing heavy work than among those doing little or no physical work.

Occupational work evaluation hastens patients' return to work because it reassures them and their primary care physicians about the safety of an earlier than customary return to work.[7] Cardiac rehabilitation programs lack control over the medical decision to advise patients to return to work after a myocardial infarction. This decision, which is fraught with perceived medicolegal liability, is generally considered to lie within the province of the physician-patient relationship.

The perceived need for coronary risk factor management has increased with the use of thrombolysis. For example, coronary arteriosclerosis may partially regress with lipid-lowering drugs.[8,9] This demonstration will doubtless stimulate the use of these agents. Smoking cessation and diet-drug management of hypercholesterolemia are important objectives in cardiac rehabilitation. These are relatively time-intensive interventions. Because Medicare provides reimbursement only for exercise training (and only three months of it), it is not surprising that these interventions are not better integrated into cardiac rehabilitation programs.

Incorporating more effective and efficient techniques for smoking cessation and diet-drug management for hypercholesterolemia might enhance the attractiveness of rehabilitation programs for physicians and patients alike. Physicians' unwillingness to relinquish responsibility for risk factor management, however, may continue to frustrate the delivery of these preventive services by cardiac rehabilitation programs. Physicians may relinquish certain aspects of management such as exercise training with which they are generally unfamiliar, or smoking cessation or the dietary management of hypercholesterolemia, for which they often manifest little enthusiasm. In contrast, drug management of hypercholesterolemia is an element of health care over which they generally prefer to maintain control, if only because of the medicolegal considerations.

In summary, the success of contemporary medical and surgical therapy for acute ischemic chest pain syndromes and a dramatic shortening of hospital stays have changed the focus of cardiac rehabilitation. Cardiac rehabilitation programs can now best serve the needs of patients with ischemic heart disease by facilitating smoking cessation and diet-drug management of hypercholesterolemia. Whether such a shift in emphasis away from exercise conditioning will attract a large number of the patients who do not presently undergo cardiac rehabilitation depends on the efficacy, convenience, and cost of risk factor modification offered by these programs. In today's increasingly competitive environment, cardiac rehabilitation programs must demonstrate to patients and physicians alike that they provide benefits not available in usual care.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Niacin Benefits

To THE EDITOR: The editorial by Malloy and colleagues in the October 1991 issue[1] graphically outlines the side effects of niacin therapy. It should dampen enthusiasm for self-medication.

What, however, is the risk/benefit ratio for niacin? Clearly, we cannot simply tell patients, "It is the only drug so far associated with increased survival in an intervention trial," as stated in the editorial.

Few patients will opt for niacin therapy if they are given a candid summary of the trial, that is, cholesterol reduction resulted in increased mortality (21.2% vs 20.9%) during niacin therapy.[2]

After the five-year trial, serum cholesterol levels *rose* to pretreatment levels when niacin was discontinued. Three years later, the treated group began to show reduced mortality (24.4% vs 25.4%), and this difference continued to widen at ten years' follow-up (52% vs 58.2%).[3]

Thus, we have an inverse relationship between cholesterol and mortality: the niacin-induced drop in cholesterol levels was associated with higher immediate mortality, and a posttherapy rise in cholesterol was followed by lower mortality.

There is no evidence that *continued* niacin therapy would result in this same improved survival, and the meta-analysis by Muldoon and associates suggests that cholesterol reduction may often result in a discouraging increase in overall mortality.[4]

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* * *

Drs Malloy and Kane Respond

To THE EDITOR: Dr Bassler's letter raises the question of the risk and benefit of hypolipidemic therapy in the context of treatment with niacin. Although he alludes to increased mortality among those treated with niacin during the Coronary Drug Project trial, the difference (21.2% vs 20.9%) in mortality is so small as to be biologically meaningless. The difference in mortality in the decade following the study was, however, impressive (and statistically significant). That the serum cholesterol levels rose when niacin was discontinued was predictable. The most reasonable explanation for the diminished mortality in the years following the trial among those who took niacin is based on our current understanding of the natural history of coronary artery disease in which most lesions tend to increase gradually in size toward the initiation of clinical events. Inhibited progression or regression of lesions during treatment with niacin could thus be expected to result in postponement of some lethal events later in life.

A number of critics of lipid-lowering therapy have based their analyses on single drug trials that achieved marginal effects on lipoproteins. Many have restricted their analyses to the relatively short trial periods. Based on the assumption, now known to be erroneous, that lesions would not regress but that progression might be inhibited, nearly all such trials were conducted on men in age groups in which new coronary events are uncommon. It is clear that limiting the analysis of benefit to the relatively small differences observed between control and treated groups in these trials greatly underestimates the benefit that would be expected if the differences in the rate of progression or regression were projected out to the later decades of life where clinical coronary events are numerous. Thus, this "delta Y tangent" effect should be the appropriate analysis of the effectiveness of lipid-lowering therapy.

Nearly every epidemiologic survey has identified a positive relationship between levels of atherogenic lipoproteins in blood and the risk of coronary artery disease. Three recently reported angiographic trials, all of which included niacin in combined drug regimens, demonstrated significant regression of coronary placques during aggressive therapy for hyperlipidemia.[1-3] These studies strongly support the lipid hypothesis that a reduction in levels of atherogenic lipoproteins in plasma can prevent or delay the emergence of clinical coronary artery disease. Therefore, treatment designed to achieve ideal levels of atherogenic lipoproteins has a strong mechanistic basis and is a rational intervention pending the availability of data from long-term studies.

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Motorcycle Helmet Use Study

To the Editor: In "Helmet Use Improves Outcomes After Motorcycle Accidents" in the October 1991 issue, Murdock and Waxman reported findings leading them to conclude that helmet use was effective in preventing death and disability from head injury in patients brought to a trauma center.[1] The authors, however, went on to state that "these data support the need for both increased public education regarding helmet use and mandatory use legislation" (p 372). It should be pointed out that although the *authors* may support such measures, the *data* did nothing of the sort. This was a study of the relationship between helmet use and trauma center outcomes. This was *not* a study of proposed interventions such as increased public education or mandatory helmet use and therefore permits no conclusions, positive or negative, to be drawn regarding such interventions. A study showing that alcohol avoidance improves hospital outcomes would not, for example, show per se that increased public education regarding alcohol use would be cost effective, or that the mandatory prohibition of alcohol would be wise public policy. As an emergency physician and motorcyclist, I believe in the value of the helmet—but I also believe that the cause of good preventive medicine will not in the end be well served by bad science.

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1. Murdock MA, Waxman K: Helmet use improves outcomes after motorcycle accidents. West J Med 1991 Oct; 155:370-372

* * *

To the Editor: Although most public health professionals (including ourselves) welcome data demonstrating that "helmet use was effective in preventing death and disability," the study by Murdock and Waxman in the October 1991 issue[1] does not do this. The flaw lies in nonrandomization: helmet-wearing motorcyclists are different from non-helmet-wearing motorcyclists. This is suggested both by intuition—those who wear helmets are probably more concerned about safety—and by Murdock and Waxman's findings: those who wore helmets were significantly less likely to be intoxicated (suggesting both better judgment about safe riding conditions and better response times), more likely to be able to pay hospital bills and to be insured (and therefore more likely to have been employed persons who were better able to maintain their motorcycles), and were slightly older (possibly suggesting more maturity). It is therefore possible that the helmeted riders may have had less serious accidents—that is, accidents occurring at lower speeds and impacts. It would also be interesting to ascertain—by examining helmets and by evaluating skull and other fracture sites—if those wearing helmets may have had fewer head injuries because they had different types of accidents and were less likely to have sustained direct head trauma, an alternative hypothesis that is suggested by the five helmeted riders who died of thoracic and abdominal injuries.

In addition to the fundamental problem of nonrandomization, the lack of denominator data is also of concern, as the authors point out (perhaps, for example, nonhelmeted riders had a greater number of minor injuries, and these riders were more likely to be taken to one of the other trauma centers in the county).

We are not espousing a randomized trial, and we are impressed by the data that are presented here. We are, however, suggesting that more modest conclusions and claims for subsequent action may be appropriate.

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* * *

Dr Waxman and Ms Murdock Respond

To the Editor: We appreciate the comments in the two letters regarding our review of outcomes in helmet-wearing and non-helmet-wearing motorcycle accident victims brought to our trauma center. While we agree that views expressed by the authors of these letters have some validity, we nonetheless stand by the conclusions we made.

Drs Frank and White correctly point out that our study was not randomized, and thus there may have been other differences between the two groups of patients besides helmet use. Hence, theoretically, helmet use may have been coincidental to outcome, while other differences between the groups were really responsible for the different outcomes. Although this is a logical possibility, it seems unlikely that any of these other variables would explain the difference in facial and head injuries that we observed in patients brought to our trauma center. Better employment, better motorcycles, or better judgment may explain why accidents might not occur and may even contribute to less severe accidents. But once a serious motorcycle accident with injury has occurred, it is difficult to imagine how these factors would protect the head and face. Rather, the use of a helmet clearly seems most relevant in this regard.

Dr Goldstein correctly points out that our study was not designed to test the effectiveness of public education or mandatory helmet use, but he implies it was "bad science" for us to suggest public education or mandatory helmet use. We strongly disagree with this implication. Dr Goldstein apparently accepts our conclusion that helmet use prevented serious injuries but challenges our suggestion that telling people about this may be of benefit. The benefits of public education are well known, and it seems irrational to suppose that education regarding helmet use would be an exception.

We base our support for mandatory helmet use legislation not only on our data but also on numerous studies demonstrating an increasing number of head injuries following the repeal of mandatory helmet-use legislation in a number of states, as referenced in our article. While helmet-use legislation is a complex political issue and Dr Goldstein is certainly entitled to his opinions, we object to his labeling our work as "bad science." The critiques he expressed appear to be based more on political bias than on scientific disagreement.

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Leg Symptoms in Veterans

To THE EDITOR: I read the article by Oboler and colleagues concerning leg symptoms in outpatient veterans in the September 1991 issue.[1]

The article does not mention spinal stenosis as a cause of leg symptoms in "outpatient veterans." The authors discuss peripheral neuropathy, peripheral vascular disease, and metabolic leg cramps. A differential diagnosis of each one of these entities would include spinal stenosis, sometimes referred to as neurogenic claudication.

A common symptomatic differentiation between lumbar spinal stenosis and the other causes of leg pains includes the dramatic relief of symptoms when the patient sits down as opposed to standing, walking, or lying down. Although neurologic findings are often meager, a computed tomographic scan or magnetic resonance imaging will usually lead to the correct diagnosis.

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1. Oboler SK, Prochazka AV, Meyer TJ: Leg symptoms in outpatient veterans. West J Med 1991 Sep; 155:256-259

* * *

Drs Oboler, Prochazka, and Meyer Respond

To THE EDITOR: As pointed out by Dr Slater, we did not address spinal stenosis in our paper on leg symptoms in veterans. Initially we planned to include claudication as one of the target symptoms. Since spinal stenosis typically presents as exertional leg pain exacerbated by spinal extension but with intact peripheral pulses, patients with spinal stenosis would likely have been included in the group with symptoms of claudication. In piloting our questionnaire, however, we found that the question, "Do you have pain in your legs when you walk that is relieved with rest?" was too nonspecific, as patients with known degenerative joint disease, radiculopathy, and peripheral vascular disease all answered in the affirmative. We therefore did not include exertional leg symptoms in our survey. We agree that spinal stenosis may be a common problem in this population.

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Response Bias

To THE EDITOR: I was dismayed to see in the August 1991 issue Baldwin and colleagues[1] cite Guadagnoli and Cunningham[2] and Sobal and Ferentz[3] in support of their remarks about response bias. Blalock and Dial[4] have challenged some of the conclusions drawn by Guadagnoli and Cunningham and by Sobal and Ferentz, especially the conclusion that low response rates are not as serious a problem as survey researchers have traditionally thought. Stated briefly, our chief objections were that lack of bias in one variable does not necessarily imply lack of bias in any other variable, and tests for univariate bias do not address the possibility of biases in bivariate or multivariate distributions.

I shall add another objection that perhaps we should have raised earlier: The results of response bias tests do not generalize from one study to another. There are stronger reasons to expect response bias in some populations, and with some survey instruments, than in others. In the case of a survey of medical students on the topic of mistreatment, one might reasonably expect a bias in favor of response by students who are both angry about mistreatment and not too repressed or distrustful to answer questions about it.

I hasten to add that this should in no way diminish the level of concern aroused by the disturbing situation that Baldwin, Daugherty, and Eckenfels describe.

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Concurrent Munchausen's and 'VIP' Syndromes

To THE EDITOR: Patients with a variety of psychiatric conditions often evoke uncomfortable feelings in their clinicians, which may interfere with objectivity and clinical judgment and thus threaten optimal care. Groves describes four kinds of provocative or "hateful" patients[1]: dependent clingers, entitled demanders, manipulative help-rejecters, and self-destructive deniers. Although clinicians are generally aware of such difficult patients, the concurrence of two provocative clinical syndromes poses an additional risk of inferior care.

Report of a Case

A 43-year-old woman presented with recurrent fever, nausea, severe back pain, and constipation. Before admission, she had contacted the hospital's fund-raising department to inform them that she was a relative of the President of the United States and a personal friend of the hospital's chief executive officer, and she requested a special suite during her stay. At that point, she was referred to the attending internist as a new patient. She related a history of many operations, including hernia repair, cholecystectomy, drainage of a subphrenic abscess, hemicolectomy, and repeated lysis of surgical adhesions. She said she was allergic to penicillin, nonsteroidal anti-inflammatory drugs, phenytoin (previously called diphenylhydantoin), and several other drugs (yet, later in the hospital course she claimed to have a history of seizures for which she requested diazepam and phenytoin). The patient was medically well informed and said that she was a physician as well as having a PhD, having attended McGill University Medical School.

On physical examination, she was tearful and had multiple abdominal scars. Examination of the buttocks revealed extensive induration and scarring, which the patient said were sites of previous biopsies for "a sclerosing disease." Screening laboratory tests revealed mild anemia and a slightly elevated thyroid-stimulating hormone level.

During her hospital course, the patient was demanding

and adamant in her requests for analgesia. Eventually two other physicians known to the patient related that she had been in and out of numerous hospitals with leg abscesses from self-injections. When offered such options as drug rehabilitation, detoxification, or psychiatric hospital admission, she declined indignantly. She did not keep any follow-up outpatient appointments.

Discussion

In addition to multiple-drug abuse, this case demonstrates characteristic features of Munchausen's syndrome,[2,3] including a dramatic presentation, history and evidence of previous hospital admissions and numerous procedures, an evasive and truculent manner, and an intense but unconvincing history. Such patients generally embellish their stories with colorful, dramatic lies. Although extensive medical knowledge is often observed in patients with Munchausen's syndrome, this patient also presented herself as a "very important person," thus leading to a VIP syndrome wherein her purported stature as someone of political and medical importance brought special staff treatment.[4]

Physicians caring for patients with either syndrome alone may experience feelings of anxiety and dread. In addition to her apparent political status, this patient's impressive medical knowledge seemed to intimidate her care givers. Patients with VIP status sometimes evoke excitement in their physicians, who gain a sense of importance from their patient's celebrity. Whether positive or negative, such feelings may cloud clinical judgment and delay appropriate care. We estimate a three-day treatment delay as a result of these concurrent and provocative syndromes.

The successful treatment of patients with both syndromes has never been described; experience with Munchausen's patients suggests that such interventions as psychotherapy, behavioral therapy, and confrontation are generally ineffective.[5] A psychiatric consultant may be helpful in confronting the patient conjointly with the patient's physician. Such confrontation should be nonpunitive with alternative treatments offered, including psychiatric hospital admission. An additional approach would be to establish a regularly updated, readily accessible registry of such patients to alert clinicians and facilitate early recognition.

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CALIFORNIA MULTISPECIALTY. Dermatologist, Radiologist, Otorhinolaryngologist, General Surgeon, Cardiologist, Internal Medicine, Pediatrician, Gastroenterologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

OB/GYN—Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE Physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

PEDIATRICIANS—Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

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BE/BC UROLOGIST to join busy 28 doctor multispecialty group practice. Excellent practice opportunity, full range of benefits, early partnership status. For more information contact Shane Spray, 1400 Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

BC/BE FAMILY PRACTITIONER, OB-competent, for nonprofit community clinic in California redwood country. Rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

INTERNIST. Immediate opening. Large, established, rapidly growing Los Angeles medical facility. High salary. Full benefits. Malpractice insurance paid. Contact Mr Miller; (213) 384-2504.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

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- OTOLARYNGOLOGY
- PEDIATRICS
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Tulare District Hospital
Physician Recruiting Office
PO Box 90112
Los Angeles, CA 90009
(800) 468-2687

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Linda Johnson, 8009 S. 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

(Continued on Page 216)

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(Continued from Page 214)

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NORTHERN CALIFORNIA—SOUTH BAY
BC/BE Family Physicians and Internists needed for:
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- Urgent Care setting.

All positions offer competitive compensation packages. For additional information please send CV to **Jan Sturges, Medical Management Services, 532 Race St, San Jose, CA 95126.**

ANESTHESIOLOGIST, BC. Immediate half-time position in Pocatello, Idaho (50,000 population). Join four MDs and seven CRNAs. All specialties except Cardiac. Full benefit package. Excellent hunting, fishing, and skiing. Home of Idaho State University. Contact Philip J. Knox, MD; (208) 234-1363, 7727 Katsilometes, Pocatello, ID 83204.

FAMILY PRACTICE, INTERNAL MEDICINE AND OB/GYN/PEDIATRIC physicians currently sought by our expanding multispecialty western client. Very competitive compensation packages. Contact The Recruitment Group, 6028 Sheridan Dr, Williamsville, NY 14221; (800) 766-STAT.

CALIFORNIA. MEDICAL ONCOLOGIST/HEMATOLOGIST BC/BE needed urgently to join a busy practice in the San Francisco east bay area. Excellent opportunity with built-in referrals. Terms are attractive and negotiable, including early full partnership. Access to ECOG/NSABP protocols through C-COP. For correspondence, FAX CV to (415) 778-3567 or call (415) 778-0679. Position available now. Also open to July '92 graduates.

PEDIATRICIAN—NORTHERN CALIFORNIA. BC/BE Pediatrician needed in foothill community. Excellent opportunity for private practice. Competitive income guarantee. Send CV to Number 256, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED

HAWAII. INTERNIST AND PEDIATRICIAN NEEDED for rural underserved area. Full-time position in nonprofit community health clinic. Desire dedicated person to work in multicultural setting. Contact Kathy Garner, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-1458.

FAMILY PRACTICE, BC/BE to join group practice in growing southwestern town. Full service clinic, 280-bed hospital. Offering competitive salary, equal call schedule, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

INTERNIST/FAMILY PRACTITIONER—Northern California. Immediate opportunity for BC/BE Internal Medicine/Family Practice. Practice associate emphasized or solo practice. Located north of San Francisco in wine country with outdoor activities. Assistance available for relocation and establishment of practice. Contact Margaret Ward, Redbud Community Hospital, Box 6720, Clearlake, CA 95422; (707) 994-6486.

BEAUTIFUL OREGON COAST. Private multispecialty cooperative with excellent facility seeking Family Practice physician to join five full-time Family Practitioners. Full spectrum of Family Practice. In-house lab, x-ray, day surgery. Contact Marce Knight, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294 or (800) 234-1231.

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PHYSICIANS WANTED

TRINIDAD, CALIFORNIA
Private Indian clinic overlooking ocean on northern California coast seeking two BC/BE Family Physicians to join two other Family Physicians. Exciting, challenging, comprehensive program, including Obstetrics. Gael Dougherty, RN, Medical Department Coordinator, UIHS, PO Box 420, Trinidad, CA 95570; (707) 677-3693.

NORTHERN CALIFORNIA. BC/BE GENERAL INTERNIST sought in rural community. Solo practice with shared call schedule. Send CV to Number 257, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ORTHOPEDIC SURGEON. University of California, San Francisco seeks a BC/BE Orthopedic Surgeon to fill a faculty/staff position at the Valley Medical Center, Fresno. The Orthopedic Department at VMC supports a busy trauma service and actively participates in teaching residents in General Surgery, Emergency Medicine, and Family Practice. This position also offers private practice opportunities in a setting within the faculty group. Competitive salary and benefits. The central California location offers affordable and enjoyable year-round recreational living. Address inquiries and CVs to Louis Conway, MD, Acting Chief of Orthopedics, 4910 E Clinton, #101, Fresno, CA 93727. EO/AA employer, women and minorities are encouraged to apply.

GENERAL SURGEON. Full-time BC/BE General Surgeon for multispecialty group in southeast Los Angeles. Office/hospital and consulting practice. Spanish a plus. Top salary, benefits, and malpractice insurance. Potential for shareholdership second year. Send CV to Craig Kaner, Administrator, All Care Medical Group, Inc., 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

(Continued on Page 217)

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PHYSICIANS WANTED

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For application and information contact:

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Santa Barbara, California 93101
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Deborah Karoff, Assistant Personnel Director

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SOUTHERN CALIFORNIA. Opportunity for part-time Emergency/Family Practice physicians at urgent care/industrial center in Orange. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled Family Practice physician to join our highly respected Urgent/Primary Care group with two beautiful Santa Cruz clinics. Flexible scheduling and a comprehensive benefit package. Rapid advancement to full partnership. Please send CV to Stuart Simon, MD, 6800 Soquel Dr, Aptos, CA 95003 and call (408) 662-3611.

FAMILY PRACTICE—CALIFORNIA, WASHINGTON, NEVADA. Private practice opportunities available with established physicians in a Seattle suburb, southern California, and Sparks, Nevada. For details, call Eloise Gusman; (800) 535-7698, or send CV to PO Box 101656, Fort Worth, TX 76185.

ONCOLOGIST WANTED. Oncologist wanted to join an Internal Medicine group in San Diego, California. Guarantee plus commission. Opportunity to join full partnership in two years. Number 250, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BC/BE FAMILY PHYSICIAN needed for large multi-specialty group in San Jose, California. Family Practice Department. Includes Internal Medicine, Pediatrics, Gynecology, minor surgery with inpatient/outpatient responsibilities. Good call coverage exists. Competitive salary and benefits offered. Call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

CALIFORNIA, PACIFIC NORTHWEST, ARIZONA. Positions in Family Practice, Internal Medicine, Orthopedics, Pediatrics and OB/GYN. Call or send confidential CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

WANTED: PHYSICIAN ADMINISTRATOR. NEW MEXICO. The Los Lunas Hospital and Training School, a 350-bed state operated facility for persons with developmental disabilities, is currently recruiting for a Physician Administrator. Located approximately 20 miles south of Albuquerque, New Mexico, we provide professional services and patient care to mentally and physically disabled clients. The job entails responsibility for general, technical direction of all service related to patient care and professional operations. Minimum qualifications include graduation from an accredited medical school and completion of an approved internship, plus four years experience in the practice of medicine, and licensure by the New Mexico Board of Medical Examiners. Salary up to $78,404 per year plus benefits; medical malpractice provided by the facility. Direct inquiries to David LaCourt, PhD, Administrator, Los Lunas Hospital and Training School, PO Box 1269; (505) 841-5264.

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SOUTHERN CALIFORNIA. FAMILY PRACTICE, BC, energetic individual for a rapidly growing three physician practice. Will need to do clinic, hospital, and long term care facilities. Excellent compensation, rapid progression to partnership. Location is 10 minutes from the ocean in a fast growing area near Oceanside. Here is a chance to practice private medicine without bureaucratic problems. Call (619) 630-2422.

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(Continued from Page 217)

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PHYSICIAN OPPORTUNITIES NATIONWIDE
For all specialities for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **G & G Physician Services, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

SALT LAKE CITY—URGENT CARE/FAMILY PRACTICE. Six year old center in upper middle class community. BC preferred, early partnership available. Great recreation area. Work Net, PO Box 26692, Salt Lake City, UT 84199.

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SAN FRANCISCO. Full-time physician for busy Occupational Medicine clinic. Superb opportunity in rapidly growing clinic. Hospital affiliation, malpractice paid. Excellent support staff. Send CV to General Manager, IMS, 1580 Valencia, #202, San Francisco, CA 94110.

PHYSICIANS WANTED

NORTHERN CALIFORNIA
San Jose's leading multispecialty group is growing. We are seeking BE/BC physicians in the following specialties:

- Orthopedic Surgery
- Internal Medicine/ General
- Physiatry
- Urgent Care
- Family Practice
- Otolaryngology
- Occupational Medicine

If you are committed to excellence and strongly motivated for success, we would like to hear from you. Please send your CV to Maureen Forrester, San Jose Medical Group, Inc, 45 S 17th St, San Jose, CA 95112; **or call (408) 282-7833.** An independent physician group affiliated with Stanford University Medical Center.

EXCELLENT OPPORTUNITY FOR BC/BE INTERNIST to join four Internists in San Jose area with future opportunity to assume practice of retiring physician(s). Exceptional income guarantee and benefit package being offered. Interested candidates call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

POSITIONS AVAILABLE FOR EMERGENCY PHYSICIANS WORKING PM SHIFTS. Hourly differential paid in addition to fee-for-service compensation. Shifts vary from seven to nine hours in length. Excellent fringe benefits. Malpractice paid. Contact Nancy C. Kendall at SPEMG, Inc, 5777 Madison Ave, #1090, Sacramento, CA 95841, or call (916) 974-3154 for more information.

VASCULAR SURGEON—BC/BE, recently trained (university program preferred) for mixed Vascular and General Surgery group practice in San Francisco. Send CV and availability to A. Aronow, MD, 45 Castro St, San Francisco, CA 94114.

PHYSICIANS WANTED

BC/BE FAMILY PRACTITIONER for satellite clinic of prestigious multispecialty group practice. Join one other Family Practitioner and one Physician's Assistant in small town setting with urban culture 20 minutes away. Generous benefit package. Send CV to Donald Benz, MD or Karen Stanton, The Vancouver Clinic Inc, PS, 700 NE 87th Ave, Vancouver, WA 98664; (206) 254-1240.

UROLOGISTS—BC/BE needed for multispecialty group practice in central California and single-specialty group in Tucson, Arizona. Excellent compensation packages and partnership opportunity. All inquiries confidential. Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

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HEMATOLOGIST/IMMUNOLOGIST—BC/BE, recently trained (university program preferred), to join busy Oncologist in San Francisco. Send CV and availability to A. Aronow, MD, 45 Castro St, San Francisco, CA 94114.

INTERNAL MEDICINE/PRIMARY CARE—BC/BE, recently trained (university program preferred) for group practice in San Francisco. Send CV and availability to A. Aronow, MD, 45 Castro St, San Francisco, CA 94114.

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BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

BC/BE GENERAL INTERNIST NEEDED. Nine physician department in 27 doctor multispecialty clinic. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

INTERNIST/FAMILY PRACTITIONER. Join progressive and well respected community clinic in desirable San Francisco/Oakland bay area. Position available for Internist or Family Practitioner with strong Internal Medicine background. Limited call, 3.5-5 day work week; salary plus fee-for-service for inpatient care. Excellent fringe benefits which include malpractice insurance. Send CV to Pat Royball, Personnel, La Clinica de la Raza, 1515 Fruitvale, Oakland, CA 94601; (510) 534-0078.

INVASIVE AND/OR NONINVASIVE BC/BE CARDIOLOGIST needed for well established private practice in Riverside, California. Salary guarantee. With partnership potential. Immediate opening available. Send CV to 3900 Sherman Dr, #B, Riverside, CA 92503, attn: Lynn.

INTERNAL MEDICINE. Internist, BC/BE, needed for well established private practice in Riverside, California. Salary guarantee. Immediate opening available. Send CV to 3900 Sherman Dr, #B, Riverside, CA 92503, attn: Lynn.

FOURTH INTERNIST/FAMILY PRACTICE MD for well loved multidisciplinary health center part of east San Francisco bay area community clinic network. 24 plus clinic hours plus share hospital call and coverage. Resident teaching and UCSF clinical affiliation possible. Call (510) 644-6060.

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EUGENE, OREGON. INTERNIST, BC/BE, to join well established 44 physician Primary Care group. Excellent schools. Abundant cultural and recreational opportunities. Near Cascade Mountains and coast. Home of University of Oregon. Please send CV to David Strutin, MD, Oregon Medical Group, 495 Oakway Rd, Eugene, OR 97401; or call (503) 342-2134.

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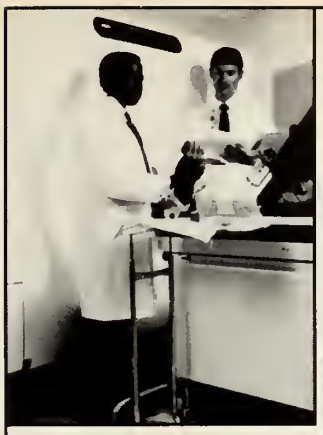

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The South Bay area provides a wide range of cultural and recreational activities, good schools, fine dining, and a congenial climate.

If you are committed to excellence and strongly motivated for success, we'd like to hear from you. Send your CV to Maureen Forrester, San Jose Medical Group,* 45 S 17th St, San Jose, CA 95112; or **call (408) 282-7833.**

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CALIFORNIA. The Lompoc Hospital District is recruiting a General Internist. Requires excellent communication and patient relation skills as well as BC/BE for certification. American training preferred. The District is facilitating a comprehensive and flexible compensation package including either a group or solo practice. The District provides a wide array of quality inpatient and outpatient services to a 50,000 resident service area through its well equipped, 60-bed acute hospital, 110-bed skilled nursing and urgent care facilities. Located between Los Angeles and San Francisco in scenic northern Santa Barbara county, Lompoc is surrounded by rolling hills and the Pacific coast shoreline. The community is family oriented and provides good schools and educational opportunities through the university level. In addition, the area supports outstanding recreational and cultural amenities. Exceptional housing opportunities exist at very affordable prices. Interested individuals should contact Scott Rhine, District Administrator, 508 E. Hickory Ave, Lompoc, CA 93436; (805) 737-3301.

OB/GYN. Full-time BC/BE OB/GYN for multispecialty group in southeast Los Angeles. Office/hospital practice. Spanish a plus. Top salary, benefits, and malpractice insurance. Potential for shareholdership second year. Send CV to Craig Kaner, Administrator, All Care Medical Group, Inc., 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

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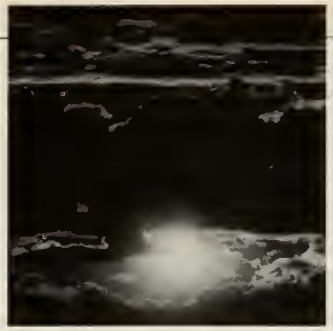
(Continued on Page 221)



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*Mule Creek State Prison, Ione
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(Continued from Page 220)

PHYSICIANS WANTED

OB/GYN. 100-BED, FULL-SERVICE HOSPITAL located 30 miles south of San Jose seeks a BE/BC OB/GYN to establish a solo practice due to area's growth. This is an outstanding opportunity for a physician wanting to establish his/her own practice. Call coverage is available and a competitive financial package is being offered. For further information, call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

CALIFORNIA MEDICAL/LEGAL DISABILITY EVALUATIONS. Opportunities available in San Jose, San Ramon, Fremont, and Capitola, California for BC physicians in Orthopedics, Psychiatry, and Cardiology with multispecialty forensic medical evaluation group. Practice limited to evaluations. California license required. Excellent opportunity to supplement income. Send inquiry and CV to Martie Woodson, QMA, 2131 The Alameda, San Jose, CA 95126.

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AMBULATORY CARE, Hayward—Modesto, California. Thriving practices, attractive facilities, competitive salary, profit-sharing, partnership with growth potential. Contact Robin Morgan, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612; (510) 835-7431. Outside of California, (800) 842-2619.

PHYSICIANS WANTED

INTERNISTS—WASHINGTON, NEVADA, TEXAS, LOUISIANA, AND FLORIDA. Private practice opportunities available with established physicians in a Seattle suburb; Reno and Las Vegas, Nevada; Victoria and McAllen, Texas; New Orleans and Shreveport, Louisiana; West Palm Beach, Plantation and Hollywood, Florida. Also need someone interested in working with HIV patients in Fort Lauderdale area. For details, call Eloise Gusman; (800) 535-7698, or send CV to PO Box 101656, Fort Worth, TX 76185.

NORTHERN CALIFORNIA RECREATION AREA. Multispecialty group has immediate opening for an Internal Medicine practitioner with a particular interest in Critical Care. Clinical activities involve full range of Internal Medicine outpatient and inpatient practice. Beautiful northern California location offers abundant recreational opportunities as well as small town living. Competitive salary and comprehensive benefit package. Please send CV to PO Box 8247, Truckee, CA 96162.

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PHYSICIANS WANTED

WEST LOS ANGELES. Dial-a-Doctor seeks BC/BE Emergency Physicians, Family Practice physicians, and Internists to answer public's medical questions by phone at $60.00 per hour plus bonus. Have fun turning your medical knowledge into cash. Send CV or inquiries to Dial-a-Doctor, MMI, 9400 Brighton Wy, Ste 414, Beverly Hills, CA 90210.

NORTHERN CALIFORNIA. Physician Recruiting Services available to solo practitioners, single and multispecialty clinics and hospitals. New, excellent placement opportunities available in OB/GYN, Dermatology and Ophthalmology; positions also in Family Practice, Internal Medicine, Orthopedic Surgery, Pediatrics, Urology and others. For information call Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (510) 376-0762.

FULL-TIME POSITION AVAILABLE. Enjoy excellent working hours, generous benefits package, no overhead, and no billing or third party reimbursement problems. California license required, Family Practitioner preferred. Call or send résumé to Northern Valley Indian Health, Inc, 2167 Montgomery St, Oroville, CA 95965; (916) 534-8440. EOE. Native Americans encouraged to apply. Deadline: June 1, 1992.

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CALIFORNIA. The Lompoc Hospital District is recruiting a Pediatrician. Requires excellent communication and patient relation skills as well as certification or eligibility for certification by the American Board of Pediatrics. American training preferred. The District is facilitating a comprehensive and flexible compensation package including either a group or solo practice. The District provides a wide array of quality inpatient and outpatient services to a 50,000 resident service area through its well equipped, 60-bed acute hospital, 110-bed skilled nursing and urgent care facilities. Located between Los Angeles and San Francisco in scenic northern Santa Barbara county, Lompoc is surrounded by rolling hills and the Pacific coast shoreline. The community is family oriented and provides good schools and educational opportunities through the university level. In addition, the area supports outstanding recreational and cultural amenities. Exceptional housing opportunities exist at very affordable prices. Interested individuals should contact Scott Rhine, District Administrator, 508 E. Hickory Ave, Lompoc, CA 93436; (805) 737-3301.

MD NEEDED. Position available for a BE/BC Pediatrician in Spokane, Washington. Exceptional office location, overflow patients available, and a liberal financial package for employment/partnership. If needed, it will be arranged for you to be flown to Spokane, Washington to be interviewed for the position. Call or send CV to Inland Empire Personnel Service, Mike Nation, Physician Placement Director, N 4407 Division, Ste 500, Spokane, WA 99207; (509) 484-3266.

YELLOWSTONE NATIONAL PARK. Physician to cover Outpatient Clinic, Emergency Room, and inpatient at Lake Hospital from Memorial Day to mid-September 1992. Send CV to Yellowstone Park Medical Services, 707 Sheridan Ave, Cody, WY 82414, or call (307) 578-2461.

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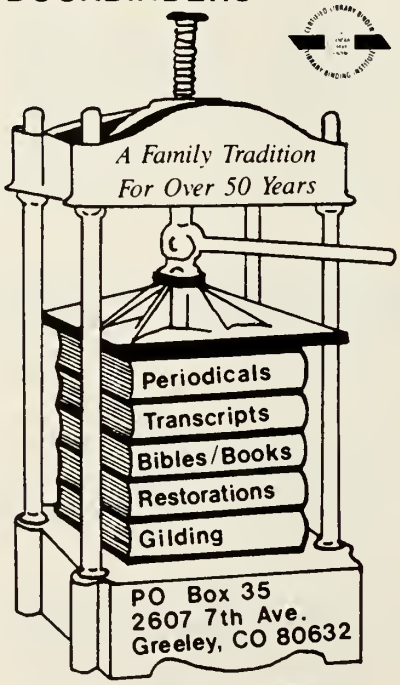

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 4-6, 1992, Scottsdale.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 13-18, 1992, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-13, 1992, Copper Mountain.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1992, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 30-August 1, 1992, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 1-3, 1992, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 23-26, 1992, Sheraton Grand Torrey Pines, La Jolla, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 14-16, 1992, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): April 24, 26, 1992, Valley River Inn; November 6-8, 1992, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. September 16-19, 1992, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 9-12, 1992, Jantzen Beach, Oregon.

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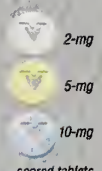

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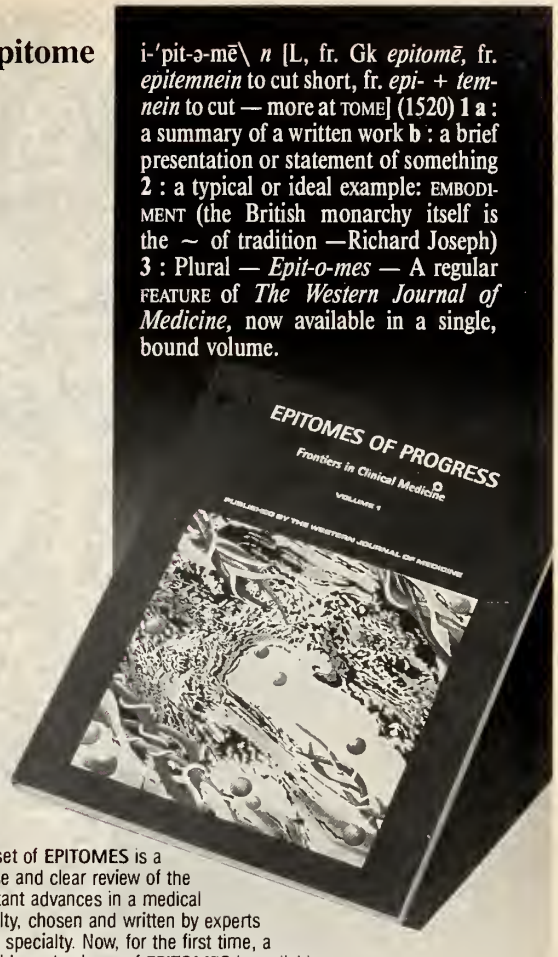

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(Bradley KA: Management of alcoholism in the primary care setting. West J Med 1992 Mar; 156:273-277)

Primary care physicians can play an important role in managing alcoholic patients. Identifying and treating alcoholism early, before it has interfered with patients' relationships and work, may increase the likelihood of prolonged recovery. Simple office interventions can help motivate patients to abstain and seek treatment. People who abuse alcohol and are unwilling to abstain can benefit from a recommendation to reduce their intake of alcohol. For alcohol-dependent patients who decide to stop drinking, primary care physicians often can manage withdrawal on an outpatient basis. Selecting an appropriate treatment program for each alcoholic patient is important, and referral to a specialist to assist in matching patients to treatments is often necessary. Primary care physicians also can help prevent relapse. Although disulfiram is of limited value, primary care physicians can support recovery by identifying coexistent psychosocial problems, helping patients to restructure their lives, and ensuring continuity of care.

PRIMARY CARE FOR ALCOHOLISM
ALCOHOLISM
ALCOHOL-DEPENDENT PATIENTS

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Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups.The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of anti-androgenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

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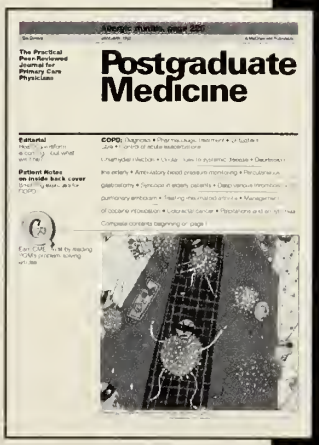

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†Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

‡Verapamil should be administered cautiously to patients with impaired renal function.

References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade: Verapamil in Focus*. New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol*. 1990;66:131-151. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow-release verapamil in essential hypertension. *Eur J Clin Pharmacol*. 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation*. 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology*. 1988;39:102S-1029.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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In Memoriam

California Medical Association

ALLEN, RICHARD G., Palo Alto. Died Sep 28, 1991, aged 77. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1938. Dr Allen was a member of the Santa Clara County Medical Association.

AMALFITANO, JOSEPH NEIL, Sacramento. Died Nov 2, 1991, aged 47. Graduate of University of Michigan Medical School, Ann Arbor, 1971. Licensed in California in 1973. Dr Amalfitano was a member of the Sacramento-El Dorado Medical Society.

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HENDY, ALLEN F., San Bernardino. Died Dec 5, 1991, aged 74. Graduate of University of Southern California School of Medicine, Los Angeles, 1947. Licensed in California in 1947. Dr Hendy was a member of the San Bernardino County Medical Society.

HERSH, SAUL T., Oakland. Died Sep 14, 1991, aged 84. Graduate of University of Minnesota Medical School, Minneapolis, 1930. Dr Hersh was a member of the Alameda-Contra Costa Medical Association.

HERZOG, GEORGE K., San Francisco. Died Jul 15, 1991, aged 78. Graduate of Stanford University School of Medicine, Stanford, California, 1938. Licensed in California in 1938. Dr Herzog was a member of the San Francisco Medical Society.

HILL, GERALD C., Riverdale. Died Nov 24, 1991. Dr Hill was a member of the Fresno-Madera Medical Society.

HOGAN, EDWARD J., JR, Burlingame. Died Dec 17, 1991, aged 64. Graduate of University of Vermont College of Medicine, Burlington, 1953. Dr Hogan was a member of the San Mateo County Medical Society.

IRVING, PETER L., South Lake Tahoe. Died Sep 5, 1991, aged 63. Graduate of Harvard Medical School, Boston, Massachusetts, 1954. Licensed in California in 1956. Dr Irving was a member of the Sacramento-El Dorado Medical Society.

KUYKENDALL, STEPHEN A., Temecula. Died Sep 23, 1991, aged 47. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1971. Licensed in California in 1982. Dr Kuykendall was a member of the Riverside County Medical Association.

LANFORD, BOB T., Fresno. Died Jan 5, 1992, aged 70. Graduate of Hahnemann Medical College, Philadelphia, Pennsylvania, 1946. Dr Lanford was a member of the Fresno-Madera Medical Society.

LAUDERDALE, JAMES M., Salinas. Died Nov 17, 1991, aged 68. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1948. Dr Lauderdale was a member of the Monterey County Medical Society.

LAWRENCE, W. SHERWOOD, Sacramento. Died Nov 5, 1991, aged 76. Graduate of Stanford University School of Medicine, Stanford, California, 1942. Licensed in California in 1948. Dr Lawrence was a member of the Sacramento-El Dorado Medical Society.

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298 **Picture Archiving and Communication Systems**
RONALD L. ARENSON, MD

299 **Shoulder Magnetic Resonance Imaging**
JOEL K. LIPMAN, MD

299 **The Imaging of Impotence**
ROGER H. THOMAS, MD

300 **Current Status of Discography**
JAMSHID TEHRANZADEH, MD

300 **Radiosurgery for Tumors and Arteriovenous Malformations of the Brain**
BRIAN R. GRIFFIN, MD

301 **Chemoembolization in the Treatment of Hepatic Malignancy**
MICHAEL J. PENTECOST, MD, and GEORGE P. TEITELBAUM, MD

301 **Vasodilator and Exercise Cardiac Perfusion Scintigraphy**
ROBERT W. HENDERSON, MD

302 **The Simplicity and Safety of Radiologically Placed Gastric Tubes**
JEFFREY C. BRANDON, MD; LARRY-STUART DEUTSCH, MD, CM; LANE KANNEGIETER, MD; and DAMON P. MILLER III, MD

ALERTS, NOTICES, AND CASE REPORTS

303 **The Sulfone Syndrome in a Patient Receiving Dapsone Prophylaxis for *Pneumocystis carinii* Pneumonia**
JANET MOHLE-BOETANI, MD; SHIVA K. AKULA, MD; MARK HOLODNIY, MD; DAVID KATZENSTEIN, MD; and GABRIEL GARCIA, MD

From the Meningitis and Special Pathogens Branch, Center for Infectious Disease, Centers for Disease Control, Atlanta, Georgia; the Department of Medicine, Tulane University Medical Center, New Orleans, Louisiana; the Veterans Affairs Medical Center, Palo Alto, California; and the AIDS Clinical Trials Unit and Clinical Gastroenterology Unit, Stanford University School of Medicine, Stanford, California.

306 **Odontoid Osteomyelitis—An Unusual Presentation of an Uncommon Disease**
JOEL RUSKIN, MD; STANLEY SHAPIRO, MD; MARIE McCOMBS, MD; HARVEY GREENBERG, MD; and EDWARD HELMER, MD

From the Division of Infectious Diseases, Department of Internal Medicine, and the Department of Radiology, Kaiser Permanente Medical Center, Los Angeles, California.

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309 **The 'No Code' Tattoo—An Ethical Dilemma**
KENNETH V. ISERSON, MD, MBA

From the Center for Clinical Medical Ethics, University of Chicago Pritzker School of Medicine, Chicago, Illinois, and the Arizona Bioethics Program, University of Arizona College of Medicine, Tucson.

313 **Letter to My Future Doctor**
FAITH FITZGERALD, MD

From the Department of Internal Medicine, Housestaff Affairs, University of California, Davis, School of Medicine, Sacramento.

314 **Ruminations of a Teaching Surgeon**
ROBERT A. CHASE, MD

Dr Chase is Chief, Division of Anatomy, Stanford University School of Medicine, Stanford, California.

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316 **Kindliness Is Next to Godliness**

316 **The Medical Waste Stream**
RONALD COHEN, PhD

Dr Cohen is Health Officer, Middle-Brook Regional Health Commission, Middlesex, New Jersey.

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COMMITTED TO EXCELLENCE

Roche Laboratories presents the winners of the 1991

Please join us in honoring these outstanding Roche sales representatives who have distinguished themselves by a truly exceptional level of professionalism, performance and dedication to quality health care.

Throughout the year, each of these award-winning individuals has consistently exemplified the Roche Commitment to Excellence, and we're proud to invite you to share in congratulating them on their achievement.

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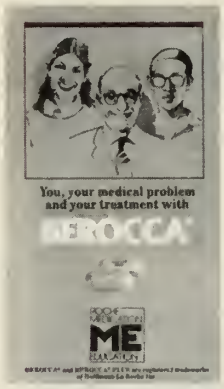

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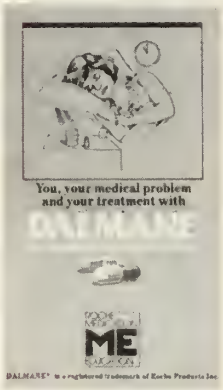

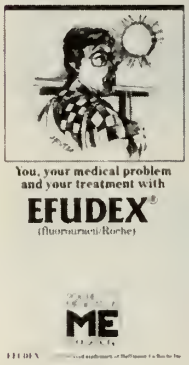

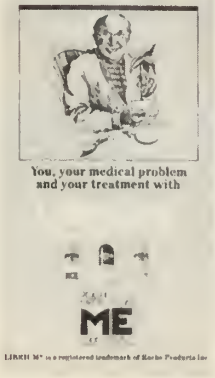

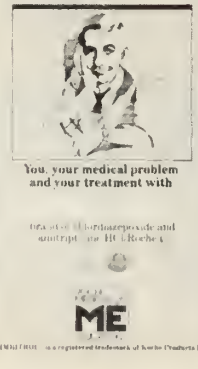

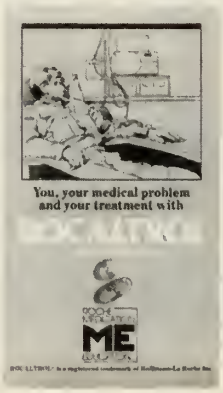

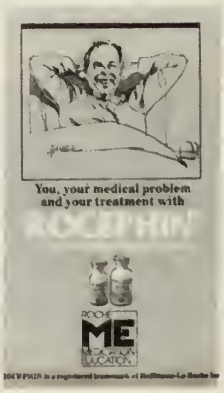

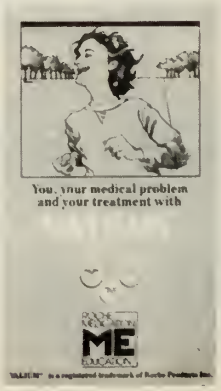

In Memoriam

(Continued from Page 237)

Lewis, Robert L., Berkeley. Died Nov 7, 1991, aged 72. Graduate of University of California, San Francisco, School of Medicine, 1938. Dr Lewis was a member of the Alameda-Contra Costa Medical Association.

McCorvey, Norborn B., San Bernardino. Died Sep 29, 1991, aged 72. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1944. Licensed in California in 1945. Dr McCorvey was a member of the San Bernardino County Medical Society.

Matthews, Vinton S., San Jose. Died Oct 18, 1991, aged 71. Graduate of Stanford University School of Medicine, Stanford, California, 1951. Dr Matthews was a member of the Santa Clara County Medical Association.

Pasmore, John L., Agnew. Died Nov 20, 1991, aged 90. Graduate of Stanford University School of Medicine, Stanford, California, 1930. Licensed in California in 1930. Dr Pasmore was a member of the Santa Clara County Medical Association.

Priest, Allen E., Sacramento. Died Aug 28, 1991, aged 81. Graduate of University of Oregon School of Medicine, Portland, 1939. Licensed in California in 1939. Dr Priest was a member of the Sacramento-El Dorado Medical Society.

Reicher, Jacob, Eureka. Died Nov 29, 1991, aged 84. Graduate of Georgetown University School of Medicine, Washington, DC, 1934. Dr Reicher was a member of the Humboldt-Del Norte County Medical Society.

Reid, Daniel A., Concord. Died Sep 10, 1991, aged 49. Graduate of University of Michigan Medical School, Ann Arbor, 1968. Dr Reid was a member of the Alameda-Contra Costa Medical Association.

Ryan, Paul A., Indio. Died June 20, 1991, aged 69. Graduate of Georgetown University School of Medicine, Washington, DC, 1946. Licensed in California in 1963. Dr Ryan was a member of the Riverside County Medical Association.

Rytand, David A., Stanford. Died Nov 24, 1991, aged 82. Graduate of Stanford University School of Medicine, Stanford, California, 1929. Licensed in California in 1933. Dr Rytand was a member of the Santa Clara County Medical Association.

Saunders, John, San Francisco. Died Dec 19, 1991, aged 88. Dr Saunders was a member of the San Francisco Medical Society.

Sayer, William J., Palo Alto. Died Oct 19, 1991. Graduate of University of Arkansas, 1948. Dr Sayer was a member of the Santa Clara County Medical Association.

Slater, Ronald B., Hayward. Died May 27, 1991, aged 71. Graduate of George Washington University School of Medicine, Washington, DC, 1946. Dr Slater was a member of the Alameda-Contra Costa Medical Association.

Somerfield, Harry, San Francisco. Died Dec 24, 1991, aged 82. Graduate of Stanford University School of Medicine, Stanford, California, 1925. Licensed in California in 1925. Dr Somerfield was a member of the San Francisco Medical Society.

Stephens, Warren C., Jr, San Mateo. Died Dec 19, 1991, aged 82. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1935. Dr Stephens was a member of the San Mateo County Medical Society.

Taggert, Merlin M., Delano. Died Nov 26, 1991, aged 85. Licensed in California in 1932. Dr Taggert was a member of the Kern County Medical Society.

Tainter, Eugene G., Sacramento. Died Nov 30, 1991, aged 81. Graduate of Stanford University School of Medicine, Stanford, California, 1942. Licensed in California in 1942. Dr Tainter was a member of the Sacramento-El Dorado Medical Society.

Vautrin, Alvin H., Orange. Died Oct 19, 1991, aged 63. Graduate of University of Southern California School of Medicine, Los Angeles, 1957. Dr Vautrin was a member of the Orange County Medical Association.

Waters, Eunice S. B., Napa. Died Oct 26, 1991, aged 84. Graduate of University of Rochester Medical School, Rochester, New York, 1933. Licensed in California in 1953. Dr Waters was a member of the Napa County Medical Society.

Wong, Wallace B., San Jose. Died Nov 23, 1991, aged 60. Graduate of Jefferson Medical College, Philadelphia, Pennsylvania, 1956. Dr Wong was a member of the Santa Clara County Medical Association.

Yaffe, Henry I., Berkeley. Died Mar 5, 1991, aged 80. Graduate of University of Minnesota Medical School, Minneapolis, 1936. Dr Yaffe was a member of the Alameda-Contra Costa Medical Association.

Denver Medical Society

Blair, James Robert. Died Sep 13, 1991, aged 78. Graduate of Tufts College Medical School, Boston, Massachusetts, 1937. Licensed in Colorado in 1939.

Garner, Frank Lake. Died Aug 21, 1991, aged 68. Graduate of University of Colorado School of Medicine, Denver, 1949. Licensed in Colorado in 1954.

Kobayashi, Thomas K. Died Oct 5, 1991, aged 77. Graduate of University of Colorado School of Medicine, Denver, 1943. Licensed in Colorado in 1943.

Livingston, Wallace H. Died Nov 1, 1991, aged 76. Graduate of University of Colorado School of Medicine, Denver, 1942. Licensed in Colorado in 1942.

Thompson, Rollin Lamoine. Died Sep 9, 1991, aged 64. Graduate of University of Colorado School of Medicine, Denver, 1949. Licensed in Colorado in 1949.

New Mexico Medical Society

Gay, Remo E., Las Cruces. Died Oct 3, 1991, aged 80. Graduate of Long Island College of Medicine, New York, 1942. Licensed in New Mexico in 1952. Dr Gay was a member of the Dona Ana County Medical Society.

McLarey, Don C., Carlsbad. Died Dec 19, 1991, aged 51. Graduate of University of Arkansas College of Medicine, Little Rock, 1965. Licensed in New Mexico in 1989. Dr McLarey was a member of the Eddy County Medical Society.

Milner, Virginia V., Albuquerque. Died Jan 1, 1992, aged 80. Graduate of University of Iowa, Iowa City, 1937. Licensed in New Mexico in 1939. Dr Milner was a member of the Greater Albuquerque Medical Association.

Thompson, Charles M., Albuquerque. Died Dec 13, 1991, aged 76. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1940. Licensed in New Mexico in 1947. Dr Thompson was a member of the Greater Albuquerque Medical Association.

ABSTRACTS MARCH 1992

(Gilden DJ, Scissors KN, Reuler JB: Disposable products in the hospital waste stream. West J Med 1992 Mar; 156:269-272)

Use of disposable products in hospitals continues to increase despite limited landfill space and dwindling natural resources. We analyzed the use and disposal patterns of disposable hospital products to identify means of reducing noninfectious, nonhazardous hospital waste. In a 385-bed private teaching hospital, the 20 disposable products of which the greatest amounts (by weight) were purchased, were identified, and total hospital waste was tabulated. Samples of trash from three areas were sorted and weighed, and potential waste reductions from recycling and substituting reusable items were calculated.

Business paper, trash liners, diapers, custom surgical packs, paper gowns, plastic suction bottles, and egg-crate pads were among the 20 top items and were analyzed individually. Data from sorted trash documented potential waste reductions through recycling and substitution of 78, 41, and 18 tonnes per year (1 tonne = 1,000 kg = 1.1 tons) from administration, the operating room, and adult wards, respectively (total hospital waste was 939 tonnes per year). We offer specific measures to substantially reduce nonhazardous hospital waste through substitution, minimization, and recycling of select disposable products.

HOSPITAL WASTE
DISPOSABLE HOSPITAL PRODUCTS
RECYCLING HOSPITAL PRODUCTS
NONHAZARDOUS HOSPITAL WASTE

(Gilden DJ, Scissors KN, Reuler JB: Disposable products in the hospital waste stream. West J Med 1992 Mar; 156:269-272)

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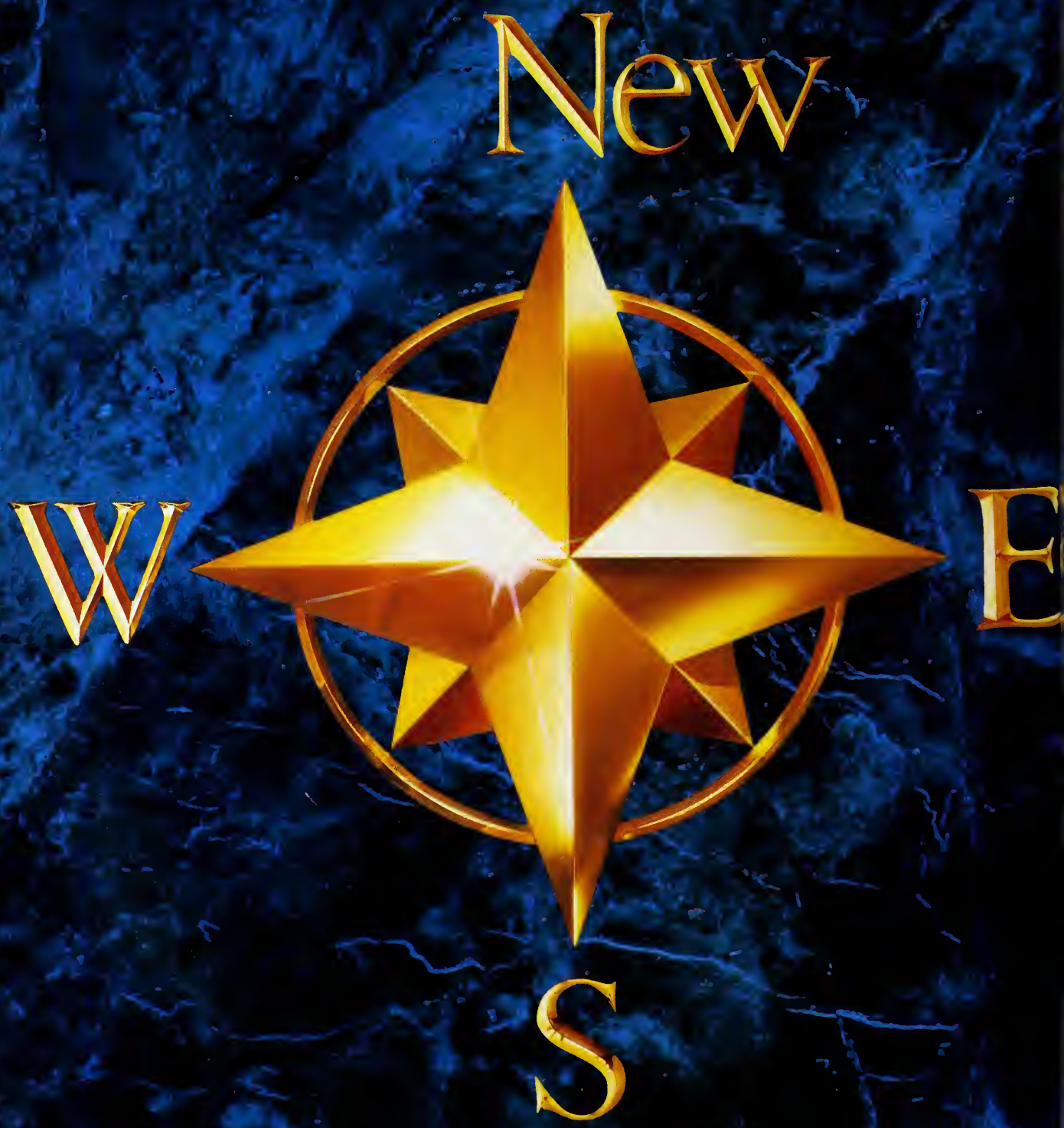
RECYCLING HOSPITAL PRODUCTS
NONHAZARDOUS HOSPITAL WASTE

Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

BRISTOL-MYERS SQUIBB INTRODUCES

A NEW DIRECTION IN LIPID MANAGEMENT

A NEW DIRECTION IN LIPID MANAGEMENT



PRAVACHOL™

pravastatin sodium 20 mg tablets

A distinct new option in cholesterol management for primary hypercholesterolemia when diet alone is inadequate

- Consistently and significantly reduces total C and LDL-C
- Positively affects other key lipids
- Excellent safety and tolerability profile
- True once-a-day dosing with or without food
- Prescribed for more than 1,000,000 patients worldwide[1]
- Studied in over 13,000 patients worldwide in clinical research[1]
- New hydrophilic structure; the clinical effect of hydrophilicity, if any, has not been established
- Administered in the active form

PRAVACHOL® is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

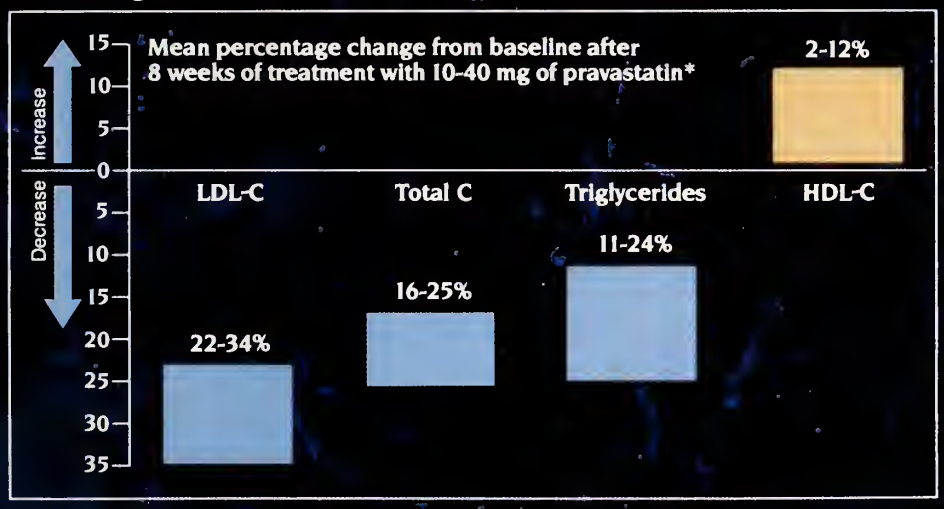
Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the final page of this advertisement.

A NEW DIRECTION IN LIPID MANAGEMENT

Effective cholesterol control

PRAVACHOL® is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Consistently and significantly reduces atherogenic LDL-C. Increases beneficial HDL-C.[2]



*Each bar represents a range of means derived from a single placebo-controlled study that included 55 patients treated with pravastatin.

Pharmacology and metabolism

- PRAVACHOL® is administered in the active form
- PRAVACHOL is hydrophilic; the clinical effect of hydrophilicity, if any, has not been established
- PRAVACHOL is selective to the primary site of cholesterol synthesis, the liver
- *In vitro* studies demonstrated that pravastatin is transported into hepatocytes with substantially less uptake into other cells

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the final page of this advertisement.

PRAVACHOL™

pravastatin sodium 20 mg tablets

A new direction in lipid management

A NEW DIRECTION IN LIPID MANAGEMENT

Safety profile promotes confidence

Possibly associated myopathy in only 1 patient in clinical trials (n>13,000)*[1]

Consider myopathy in any patient with diffuse muscle pain, tenderness, or weakness, particularly with malaise or fever. Advise patients to promptly report these symptoms. Discontinue pravastatin if myopathy is diagnosed or suspected.

In clinical studies, significant elevations of liver enzymes have been uncommon

- Increases in serum transaminase (greater than three times the upper limit of normal on two or more occasions) were seen in 1.3% of patients treated over an average of 18 months
- Elevations were generally reversible over time in patients discontinued from pravastatin; patients with biochemical findings were usually asymptomatic
- Active liver disease *or* unexplained transaminase elevations are contraindications to the use of pravastatin
- Liver function should be monitored before treatment and at recommended intervals–every 6 weeks for the first 3 months, every 8 weeks for the remainder of the first year, and periodically thereafter (e.g., at about 6-month intervals)

*A second patient developed myopathy when clofibrate was added to a previously well-tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the final page of this advertisement.

PRAVACHOL™

pravastatin sodium 20 mg tablets

A new direction in lipid management

A NEW DIRECTION IN LIPID MANAGEMENT

Well tolerated...

A side-effect profile generally comparable to placebo

Low incidence of side effects

Adverse clinical events attributed to study drug:	PRAVACHOL® (n = 900)	Placebo (n = 411)
Headache	1.7%*	0.2%
Cardiac chest pain	0.1	0.0
Rash	1.3	0.9
Nausea/vomiting	2.9	3.4
Diarrhea	2.0	1.9
Abdominal pain	2.0	3.9
Constipation	2.4	5.1
Flatulence	2.7	3.4
Heartburn	2.0	0.7
Fatigue	1.9	1.0
Chest pain	0.3	0.2
Localized pain	1.4	1.5
Myalgia	0.6	0.0
Dizziness	1.0	0.5
Urinary abnormality	0.7	1.2
Rhinitis	0.1	0.0
Cough	0.1	0.0

*Statistically different from placebo

Discontinuation rate from pravastatin (1.7%) was not statistically different from that of placebo (1.2%).

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the final page of this advertisement.

PRAVACHOL™

pravastatin sodium 20 mg tablets

A new direction in lipid management

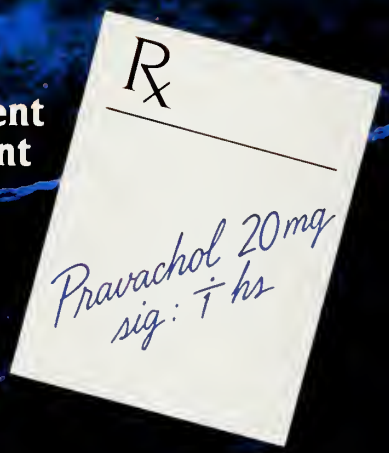
BRISTOL-MYERS SQUIBB INTRODUCES

A NEW DIRECTION IN LIPID MANAGEMENT

New

PRAVACHOL™

pravastatin sodium 20 mg tablets



Provides an exceptionally convenient regimen in cholesterol management —once-a-day bedtime dosing

PRAVACHOL® offers true once-a-day dosing at bedtime, with or without food.

Usual dose: 20 mg at bedtime, with or without food

Dosage range:
10-40 mg. Available in 10 and 20 mg tablets.

Excellent monotherapy for a wide range of patients

PRAVACHOL is suitable for patients with primary hypercholesterolemia (Types IIa and IIb) with a cholesterol-lowering diet when diet alone has not been adequate.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the final page of this advertisement.

References: 1. Data on file, Bristol-Myers Squibb. 2. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

Bristol-Myers Squibb Company

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PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% ot patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life (t½) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin*: See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL), *cimetidine, nicotinic acid*, or *probucol*, no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥ 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p < 0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area ($mg/meter^2$). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interactions**.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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1. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

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8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

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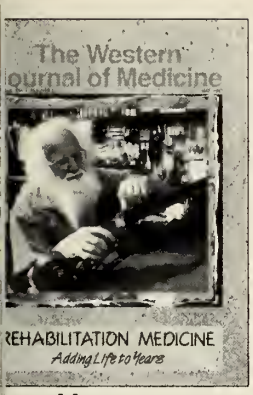


MAY 1991

REHABILITATION MEDICINE: *Adding Life to Years*

EDITED BY JULIE G. MADORSKY, MD

- REHABILITATION IN RHEUMATIC DISEASES *Mary L. Jurisson*
- REHABILITATION OF OCCUPATIONAL LOW BACK PAIN *Gerald P. Keane*
- HIV INFECTION: IMPLICATIONS FOR REHABILITATION MEDICINE *Jon A. Mukand*
- PAIN CENTERS: ORGANIZATION AND OUTCOME *Sridhar V. Vasudevan and N. Timothy Lynch*
- USE IT OR LOSE IT: THE HAZARDS OF BED REST AND INACTIVITY *Paul J. Corcoran*
- CEREBRAL PALSY *Gabriella E. Molnar*
- REVERSING DISABILITY OF IRREVERSIBLE LUNG DISEASE *Brian L. Tiep*
- SEX AND DISABILITY ARE NOT MUTUALLY EXCLUSIVE *George Szasz*
- WORKER REHABILITATION PROGRAMS: SEPARATING FACT FROM FICTION *Andrew J. Haig and Suzanne Penha*

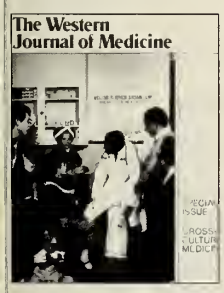
MAY 1990

Addiction Medicine and the Primary Care Physician

(3RD PRINTING)

- OVERVIEW OF ADDICTION MEDICINE *David Smith, Editor/Founder, Haight-Ashbury Free Clinic*
- CHEMICAL DEPENDENCE AND THE WORK PLACE *John Osterloh and Charles Becker*
- THE DISEASE CONCEPT OF ALCOHOLISM *John Wallace*
- COGNITIVE IMPAIRMENTS IN RECOVERING ALCOHOLICS *George Fein*
- SUBSTANCE ABUSE AND PULMONARY PATHOLOGY *Donald Tashkin*
- SPECIAL POPULATIONS: THE ADOLESCENT *Martha Morrison*
- METHADONE MAINTENANCE IN THE TREATMENT OF OPIOID DEPENDENCE *Joan Zweben*
- TREATMENT OF NICOTINE DEPENDENCE IN THE CHEMICALLY DEPENDENT PATIENT *Karen Sees*
- PHARMACOLOGIC APPROACHES TO THE TREATMENT OF COCAINE DEPENDENCE *Wanda A. Taylor and Mark S. Gold*

Cross-cultural Medicine

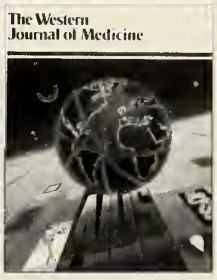


M. Margaret Clark, PhD
Special Issue Editor, 1983
3rd printing

Women and Medicine

Linda Hawes Clever, MD
Special Issue Editor, 1988

AIDS—A Global Perspective

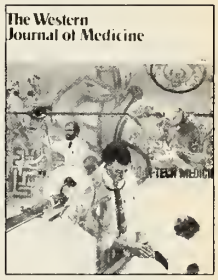


Jonathan M. Mann, MD
Special Issue Editor, 1987

Medical Informatics

Marsden S. Blois, MD
Special Issue Editor, 1986

High-Tech Medicine



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Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

March 19-20—**Clinical Reviews 1992.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Thurs-Fri. Contact: Mayo Clinic-Scottsdale.

March 21—**Primary Management of Common Cardiovascular Diseases.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Sat. Contact: Mayo Clinic-Scottsdale.

March 21—**ENT for the Primary Care Physician.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Sat. Contact: Mayo Clinic-Scottsdale.

March 23-25—**Perspectives in Hepatobiliary and Pancreatic Surgery.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Fri-Sun. Contact: Mayo Clinic-Scottsdale.

March 27-28—**Pediatric Imaging Update.** University of California, San Francisco, School of Medicine at Camelback Inn, Scottsdale. Fri-Sat. Contact: (415) 476-5731.

March 28-30—**Electromyography in Clinical Practice.** Mayo Clinic-Scottsdale at Ashton B. Taylor Auditorium, Mayo Clinic-Scottsdale. Sat-Mon. Contact: Mayo Clinic-Scottsdale.

March 30-April 3—**Radiology Spring Training.** University of California, San Francisco, School of Medicine at Camelback Inn, Scottsdale. Mon-Fri. Contact: (415) 476-5731.

June 4-6—**Arizona Medical Association—Annual Meeting.** Scottsdale. Thurs-Sat. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For more information on accreditation or certification, please write to the above address.

ALLERGY

March 27-28—**Asthma and Allergy in the 1990s.** Medical Education Resources at Wyndham Hotel, Palm Springs. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

ANESTHESIOLOGY

March 21-22—**Postgraduate Assembly.** Los Angeles County Society of Anesthesiologists at Sheraton Universal Hotel, Universal City. Sat-Sun. $200. Contact: Michael Carlson, 1903 Redondo Ave, Long Beach 90804. (213) 597-2661.

March 21-26—**20th Obstetric Anesthesia Conference.** Ohio State University Hospitals at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

May 17-22—**Anesthesiology Review Course.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

CARDIOLOGY

March 20-21—**Cardiac Diagnostic Methods & Risk Management.** Medical Education Resources at Caesars Palace, Las Vegas, Nevada. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

April 4—**Practical Cardiology for the '90s.** Grossmont Hospital at La Mesa. Sat. Contact: Karen Hamilton, PO Box 158, La Mesa 91944-0158. (619) 589-4168.

April 6-11—**31st Annual Cardiology Retreat.** Scripps Clinic and Research Foundation at Rancho Santa Fe. Mon-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 21-23—**2nd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 1-2—**2nd International Symposium on Thrombolytic Therapy in Acute Ischemic Stroke.** Scripps Clinic and Research Foundation at San Diego Marriott, La Jolla. Fri-Sat. Contact: Scripps Clinic, Box 403C, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

(Continued on Page 262)

Venous Ulcers.

Accelerated non-surgical treatment for the most advanced cases.

The physicians at Vein Clinics of America have successfully treated venous leg ulcers—including advanced cases—in our offices without the use of surgical procedures.

Our accelerated ambulatory treatment program includes: 1) Healing the ulcer itself by daily isometric application of compression therapy; 2) Addressing the underlying cause and preventing recurrence through injection sclerotherapy of incompetent perforating veins and refluxing varicose veins.

Rapid closing of ulcer.

The common denominator of most leg ulcers is venous pump failure with edema. Our treatment first removes the edema and heals the ulcer through the application of isometric compression bandaging. This increases venous outflow during ambulation, resulting in improved pump action at the calf muscle.

Initially patients are seen daily—then less frequently. This program produces the fastest response, with extreme cases healing as rapidly as the case detailed in photos on this page. Other advantages include immediate ambulation, rapid elimination of pain and drainage and high patient acceptance.

Before treatment. Patient shows chronic ulcer with subcutaneous tissue damage from years of inflammation.

Effective long-term healing.

Once the ulcer has healed and other problems such as edema and dermatitis are under control, the second phase of treatment can address prevailing underlying causes. Refluxing venous trunks, tributaries and incompetent perforating veins are eliminated by injection compression sclerotherapy, often guided by Duplex Color Ultrasound.

This selective fibrosis process improves the venous pump, resulting in long-term healing and lowered recurrence of leg ulcers.

Proven treatment program with documented results.

This treatment protocol was developed over 10 years of clinical experience, with favorable results on over 200 leg ulcer patients.

Many patients had previous surgery with skin grafting and vein stripping. But our two-step protocol provided more effective healing. This is because the treatment is directed at the underlying cause, the venous pump failure.

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After one week of isometric compression bandaging.

After two weeks.

Ulcer closed in three weeks.

One year later, following large vessel sclerotherapy.

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(Continued from Page 260)

May 26-28—**2nd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

May 30—**Regression of Coronary Artery Disease.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

August 13-15—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $325-$425. Contact: UCSF.

DERMATOLOGY

July 14-18—**Dr. Hugh Greenway's Eighth Annual Conference: Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation at UCSD Campus and Scripps Clinic, La Jolla. Wed-Sat. 36 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

July 30-August 1—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 24 hrs. $425. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

August 10-12—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

March 16-20—**Emergency Medicine Symposia II.** UCSD at Basic Science Building. Mon-Fri. Contact: UCSD.

March 20-21—**Advances in Emergency Medicine: Toxicology and Infectious Diseases.** UCLA at Hotel del Coronado. Fri-Sat. 13.5 hrs. $125. Contact: UCLA Extension.

April 1-4—**8th Annual Advances in Emergency Medicine.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Sat. $455. Contact: UCSF.

May 6-10—**14th Biannual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 18 hrs. $200-$435. Contact: UCSD.

May 11-15—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. Contact: UCSD.

June 22-26—**Emergency Medicine Symposia III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. Contact: UCSD.

August 17-21—**Emergency Medicine Symposia II.** UCSD at Basic Science Building. Mon-Fri. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

March 25-27—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF. Wed-Fri. 15.5 hrs. Contact: UCSF.

March 27-28—**Peripheral Vascular Disease: Noninvasive Diagnosis for Primary Care Physicians.** Medical Education Resources at Doubletree Resort at Desert Princess Country Club, Palm Springs. Fri-Sat. 12 hrs. Contact: Laurie Christopher, (303) 465-6402.

April 3-4—**Peripheral Vascular Disease: Noninvasive Diagnosis for Primary Care Physicians.** Medical Education Resources at Caesar's Palace, Las Vegas, Nevada. Fri-Sat. Contact: Laurie Christopher, (303) 465-6402.

April 4—**Cardiology for Primary Care.** UCDMC at Cancer Center Auditorium. Sat. Contact: UCD.

April 4-11—**5th Annual Primary Care Medicine: Update 1992.** UCSF at Maui Intercontinental, Wailea, Maui, Hawaii. 1 week. $540. Contact: UCSF.

April 9-11—**Advances in Rheumatology for Primary Care Physicians.** UCSF at Le Meridien Hotel, San Francisco. Thurs-Sat. $240. Contact: UCSF.

April 10-12—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Vacation Village, San Diego. Fri. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 15-20—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Marriott Hotel, Newport Beach. Mon-Sat. Contact: UCI.

July 6-9—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

August 7-9—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 21-23—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 21-23—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Loews Coronado Bay Resort, Coronado Island, San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

GERIATRICS

March 16-17—**Exercise in Geriatric Care.** VA Sepulveda Medical Center at Burbank. Mon-Tues. Contact: Symposium Secretary, VA Medical Center, GRECC (11E), 16111 Plummer St, Sepulveda 91343. (818) 895-9311.

INFECTIOUS DISEASES

April 25—**HIV Update.** UCDMC at Cancer Center Auditorium. Sat. Contact: UCD.

April 29-May 1—**13th Annual Advances in Infectious Diseases.** UCSF at San Francisco. Wed-Fri. $400. Contact: UCSF.

May 6-8—**13th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. $400. Contact: UCSF.

INTERNAL MEDICINE

March 20-26—**Internal Medicine 1992: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado. Fri-Thurs. 54 hours. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

May 11-15—**20th Annual Advances in Internal Medicine.** UCSF at Ritz-Carlton Hotel, San Francisco. Mon-Fri. 33 hrs. $610. Contact: UCSF.

June 22-26—**20th Annual Advances in Internal Medicine.** UCSF at Cole Hall Parnassus Campus. Mon-Fri. 32 hrs. $610. Contact: UCSF.

August 29-September 3—**10th Comprehensive Nephrology Review Course.** UCLA at Beverly Hilton Hotel, Beverly Hills. Sat-Thurs. 51 hrs. $850. Contact: UCLA Extension.

NEUROLOGY

July 30-August 1—**New Advances in Common Neurological Disorders.** UCSD at Catamaran Hotel, San Diego. Thurs-Sat. Contact: UCSD.

OB/GYN

April 2-4—**Gynecologic Surgery.** Memorial/UCI Center for Health Education at Marquis Hotel, Palm Springs. Thurs-Sat. Contact: UCI.

April 2-4—**Ultrasound Update.** Memorial/UCI Center for Health Education at Bally's Hotel, Las Vegas. Thurs-Sat. Contact: UCI.

April 8-12—**Pacific Coast Fertility Society: Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Director of Medical Education, 12760 La Mirada Blvd, Ste 220, La Mirada 90638. (213) 947-7068.

June 5-7—**Advanced Fetal Heart Rate Monitoring.** Memorial/UCI Center for Health Education at Radisson Hotel, Palm Springs. Fri-Sun. Contact: UCI.

July 29—**10th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Wed-Sat. Contact: UCI.

OCCUPATIONAL/ENVIRONMENTAL

April 3-4—**Management of Occupational Health Problems in Primary Care Settings.** University of California Berkeley at Sunnydale Hilton Hotel. Fri-Sat. 11 hrs. $275. Contact: Mary Hughes, (510) 642-5507.

June 5-6—**Occupational and Environmental Medicine.** UCD. Fri-Sat. Contact: UCD.

July 26-31—**Sports Medicine.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

ONCOLOGY

March 20-21—**Non-palpable Breast Cancer: Diagnosis and Management.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. 8 hrs. $140. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

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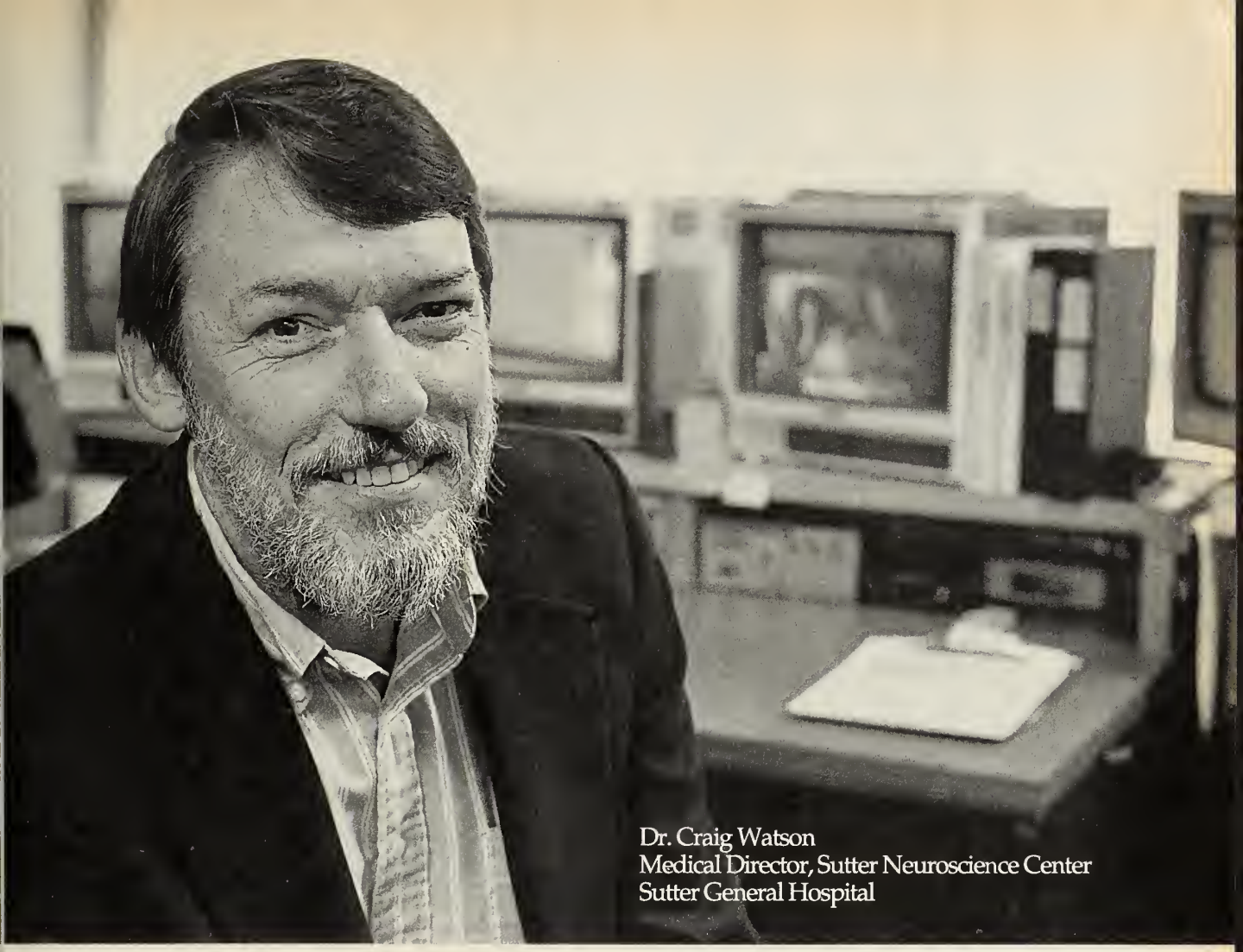

Dr. Craig Watson
Medical Director, Sutter Neuroscience Center
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The four-bed unit, which is the largest and most complete in the region, is designed for the comfort of the patients, who may need to be hospitalized for up to a week. Rooms are outfitted with a television, VCR and personal exercise equipment.

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Sutter Neuroscience Center

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Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 262)

April 30-May 3—**Breast Cancer Conference.** Memorial/UCI Center for Health Education at Hyatt Regency, Long Beach. Thurs-Sun. Contact: UCI.

OPHTHALMOLOGY

May 15-16—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 403C, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

ORTHOPEDICS

March 15-20—**The Spine: Current Concepts of Diagnosis and Treatment.** Vanderbilt University Medical Center Department of Orthopaedics at Grand Hyatt Wailea, Maui, Hawaii. Sun-Fri. $575. Contact: The Spine/Current Concepts, c/o Unconventional Inc, 3960 Park Blvd, Ste E, San Diego 92103. (619) 692-9115.

June 14-19—**16th Annual Fingers to the Toes.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. Contact: UCD.

PATHOLOGY

March-May 1992—**Bay Area Seminars in Cytopathology: 1992.** UCSF at Health Sciences West on Campus. Thursdays. 10 hrs. $150. Contact: UCSF.

April 11—**7th Annual Conference: New Treatment in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 16—**Fine Needle Aspiration Basic Tutorial.** UCSF. Sat. 12 hrs. $650. Contact: UCSF.

May 21-22—**Curent Issues in Anatomic Pathology: 1992.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Fri. 13 hrs. $325. Contact: UCSF.

August 7-8—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD at La Jolla. Fri-Sat. 15 hrs. Contact: Daniel Gormley, MD, 412 W Carroll Dr, Ste 207, Glendora 91740. (818) 963-7684.

August 9-15—**12th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton, Mauna Lani Kohala Coast, Big Island of Hawaii. Sun-Sat. 27 hrs. $950. Contact: UCSF.

PEDIATRICS

April 24-26—**1992 West Coast Regional Conference on Pediatric Psychology.** UCSF at Union Square Holiday Inn, San Francisco. Wed-Fri. Contact: UCSF.

May 14-16—**25th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $325. Contact: UCSF.

June 26-28—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Wed-Fri. Contact: Continuing Education, (619) 576-4072.

August 24-26—**Pediatrics Update: 1992.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

PSYCHIATRY

March 28—**The Psychiatric Aspects of Neurological and Medical Illness.** Southern California Psychiatric Society at Biltmore Hotel, Los Angeles. Sat. 6 hrs. Contact: SCPS, 2425 Colorado Ave, Ste 314, Santa Monica 90404. (310) 315-7233.

April 10-11—**The Cutting Edge 1992: Erotic Mysteries—Intimacy, Sexuality and Gender in the '90s.** UCSD at Omni Hotel, San Diego. Fri-Sat. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

April 10-14—**The Power of the Art—Suggestive Therapeutics: An Introduction to Medical Hypnosis.** UCSD at Mission Bay Hilton, San Diego. Fri-Tues. Contact: UCSD.

April 23-24—**11th Annual Conference on Child Abuse and Neglect.** UCDMC at Radisson Hotel, Sacramento. Thurs-Fri. 12 hrs. $175. Contact: UCD.

August 4-9—**Neuropsychiatric Aspects of Politics and Politicians.** American Academy of Family Physicians and Southern California Neuropsychiatric Institute at Mauna Kea Beach Hotel, Kamuela. Tues-Sun. 22.5 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

(Continued on Page 265)

Current Perspectives in Cardiac Transplantation

April 10, 1992
Hoag Memorial Hospital Presbyterian
Newport Beach, California

Hoag Heart Institute • Fifth Annual Symposium

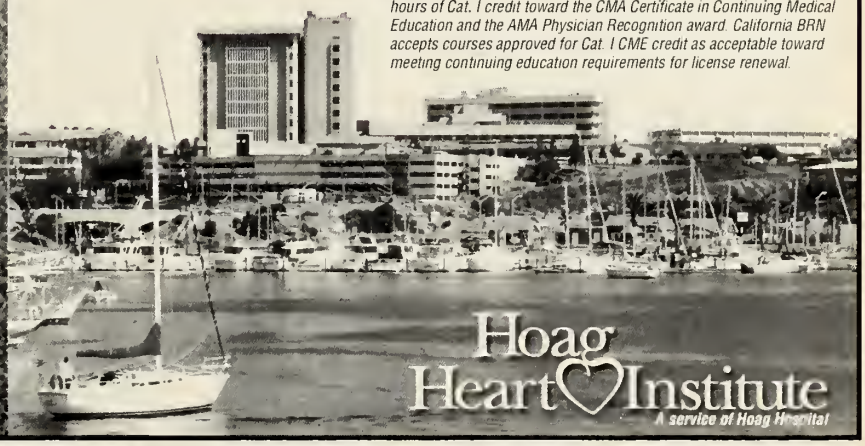
Designed for physicians and other health care professionals, this symposium will address current topics in this rapidly growing field of medicine, including current therapies in organ transplantation, appropriate terms for approaching the potential donor family, treatment modalities, analysis of common post-transplant problems and research involved in improving current immunosuppressive therapies.

Hoag Heart Institute Faculty members will be joined by guest speakers, including:

- **Norman Shumway, MD, PhD**, Professor and Chair of Cardiovascular Surgery, Stanford University Medical Center
- **Robert Mendez, MD, FACS**, USC Medical Center and President of United Network of Organ Sharing

Registration: For registration information, call Hoag Heart Institute at **714-760-2095.** Registration deadline is **April 5, 1992.** Fees are $50.00 for individuals, $30.00 per person for groups of three or more.

Accreditation: *CMA accredited provider. Physicians may report up to five hours of Cat. I credit toward the CMA Certificate in Continuing Medical Education and the AMA Physician Recognition award. California BRN accepts courses approved for Cat. I CME credit as acceptable toward meeting continuing education requirements for license renewal.*



CONTINUING MEDICAL EDUCATION

(Continued from Page 264)

August 7-11—**The Power of the Art—Suggestive Therapeutics: An Introduction to Medical Hypnosis.** UCSD at Mission Bay Hilton, San Diego. Fri-Tues. Contact: UCSD.

RADIOLOGY

March 21-23—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. 15 hrs. $350. Contact: UCSF.

March 22-27—**MRI Workshop in Hawaii: 1992.** Queens Medical Center at Kea Lani Hotel, Wailea, Hawaii. Sun-Fri. 37 hrs. $595. Contact: Susan Block, Queens Medical Ctr, 1301 Punchbowl St, Honolulu, HI 96813. (808) 547-4544.

March 23-27—**35th Annual Diagnostic Radiology Postgraduate Course.** UCSF at Fairmont Hotel, San Francisco. Mon-Fri. 35.5 hrs. $595. Contact: UCSF.

March 26-29—**Magnetic Resonance Spectroscopy on In Vivo: Tutorial and Workshop.** Thurs-Sun. 19 hrs. $100-$200. Contact: UCSF.

April 5-10—**Diagnostic Imaging: 1992.** UCSF at Hyatt Regency, Kauai, Hawaii. Sun-Fri. 22.5 hrs. $595. Contact: UCSF.

April 5-10—**General Radiology Review Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sun-Fri. 40 hrs. $425. Contact: Darryl Bailey (213) 825-8763.

April 19-24—**Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $470. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 25—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $125. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

May 4-8—**MRI: A State of the Art Clinical Review.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Mon-Fri. 23.5 hrs. $540. Contact: UCSD.

May 8-10—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 15 hrs. $400. Contact: UCSD.

May 18-22—**Practical Body Imaging: US, CT, and MRI in the 1990s.** UCSF at Marriott's Tenaya Lodge at Yosemite. Mon-Fri. 21 hrs. $595. Contact: UCSF.

May 21-24—**Doppler and Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Thurs-Sun. 21.5 hrs. Contact: UCSD.

June 4-6—**Interventional Hepatobiliary Radiology: Percutaneous Portacaval Shunts, Biliary Stents, Tumor Chemoembolization, Lithotripsy.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17.5 hrs. $425. Contact: UCSF.

June 4-6—**Vascular Stents 1992: A Comprehensive Symposium.** Scripps Clinic and Research Foundation, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 17-19—**Vascular Imaging and Intervention for the '90s.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Fri-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-22—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Mon-Wed. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-24—**Clinical Imaging for the Non-Radiologist.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Quail Lodge, Carmel. Thurs-Sun. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 27-August 1—**Advanced Neuro MRI—Beyond Spin Echo and Musculoskeletal MRI.** Hoag Memorial Hospital Presbyterian at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Sat. 32 hrs. $645. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 10-14—**Radiology & Clinical Correlation for Non-Radiologists.** UCSD at Hotel Del Coronado, San Diego. Mon-Fri. Contact: UCSD.

(Continued on Page 266)

(Continued from Page 265)

SLEEP MEDICINE

April 3-4—**Pharmacotherapeutics in Clinical Sleep Medicine.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

SURGERY

March-May 1992—**Temporal Bone Surgical Dissection Courses.** House Ear Institute at Los Angeles. 6 days each. 53 hrs. $1100. Contact: Antonio De la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext 7079.

March 18-21—**Surgical Challenges in the Head and Neck: A Dissection Course Emphasizing Contemporary Strategies.** UCSD at Basic Science Bldg, La Jolla. Wed-Sat. Contact: UCSD.

March 19-22—**42nd Annual Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: SGS, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

March 26-28—**Symposium on Aesthetic Surgery of the Face.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 18 hrs. $800. Contact: UCSF.

March 29-April 2—**29th Annual Controversial Areas in General Surgery.** UCLA at Hyatt Regency Suites, Palm Springs. Sun-Thurs. 14.5 hrs. $445. Contact: UCLA Extension.

April 2-3—**General Thoracic Surgery.** American College of Chest Physicians at Caesar's Palace Hotel, Las Vegas, Nevada. Thurs-Fri. 13 hrs. $325. Contact: ACCP, PO Box 93826, Chicago, IL 60673. (800) 343-2227.

April 2-4—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 15.5 hrs. $325. Contact: UCSF.

April 2-4—**12th Annual Meeting and Scientific Sessions of the International Society for Heart Transplantation.** UCSD at San Diego Marriott. Thurs-Sat. 15.5 hrs. $325. Contact: UCSD.

June 25-27—**9th Annual Meeting on Arthroscopic Surgery of the Shoulder.** UCSD and Tri-City Orthopaedic Surgery Medical Group at Hyatt Regency, La Jolla. Thurs-Sat. Contact: James Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 940-2066.

May 7-8—**Advanced Techniques in Laparoscopic Surgery for the General Surgeon.** UCD. Thurs-Fri. 15 hrs. Contact: UCD.

GENERAL/MULTIDISCIPLINARY

April 2-4—**Medicine Today.** UCSD at Price Center. Thurs-Sat. Contact: UCSD.

April 9-13—**Lactation Educator Training Programs.** UCLA at Westwood. 22.5 hrs. $725. Contact: UCLA.

May 4-7—**The Best Approach 1992: Effective and Efficient Strategies in Pulmonary Medicine, Sports Medicine, Cardiology, Radiology and More.** Group Health Cooperative at Royal Waikoloan, Kohala Coast, Hawaii. Mon-Thurs. 20 hrs. $350. Contact: Group Health Cooperative, CX5, 201 16th Ave East, Seattle, WA 98112. (206) 326-3441.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

March 15-20—**The Rocky Mountain Vascular Disease Symposium.** Medical Education Collaborative at The Camberley Club Hotel, Beaver Creek Resort. Sun-Fri. Contact: Laurie E. Christopher, (303) 465-6402 or (800) 442-6632.

March 16-19—**Nineteenth Annual Neonatal and Infant Respiratory Symposium.** Ohio State University Hospitals at Marriott Mark Resort, Vail. Mon-Thurs. Contact: Arlene Rogers, Ohio University Hospitals, (614) 293-8487.

March 21-28—**Headache and Facial Pain Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 21-28—**Fourth Annual Colorado Geriatrics Overview/Board Review.** University of Colorado School of Medicine at Iron Horse Resort, Winter Park. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

April 23-26—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

April 25—**Second Annual Women's Health Care Issues Conference.** Children's Hospital at University Hospital, Denver. Sat. Contact: Trish Beachy, (303) 270-8376.

May 4-8—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

May 8-9—**A Caring Affair.** Children's Hospital, Denver. Fri-Sat. Contact: Angela Pollack, (303) 861-6506.

June 12-13—**Fifth Annual Summer in the Mountains Conference.** Children's Hospital of Denver in Gunnison. Fri-Sat. Contact: Mary Haley, (303) 861-6946 or (800) 225-0010.

June 19-20—**Neonatal Resuscitation Course.** Children's Hospital of Denver in Laramie, Wyoming. Fri-Sat. Contact: Lois Pine, (303) 777-7166.

June 23-25—**Community Health Traineeship.** Children's Hospital, Denver. Tues-Thurs. Contact: Pat Winter, (303) 861-6668.

July 9—**Cultural Considerations in Perinatal Nursing.** Children's Hospital at University Hospital, Denver. Thurs. Contact: Trish Beachy, (303) 270-8376.

August 17-21—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

September 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

September 16-17—**Neonatal Resuscitation Hospital-Based Instructor Course.** Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

September 17, 24, October 1, 8—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Four consecutive Thursdays. Contact: Trish Beachy, (303) 270-8376.

October 23-24—**Fifteenth Annual Perinatal Conference.** Children's Hospital of Denver in Fort Collins. Fri-Sat. Contact: Sharon Adams, (303) 861-6946 or (800) 225-0010.

November 19-22—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

November 30-December 4—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

IDAHO

March 20—**Idaho Thoracic Society—Annual Medical Symposium.** St Alphonsus Regional Medical Center, Boise. Fri. Contact: Bill Smith, Program Director, Idaho Thoracic Society, 1111 S Orchard, Ste 245, Boise, ID 83705. (208) 344-6567.

July 30-August 1—**Idaho Medical Association—Annual Meeting.** Coeur d'Alene. Thurs-Sat. Contact: Idaho Medical Assn, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

(Continued on Page 327)

THE ART AND SCIENCE OF

VOICE CARE

SYMPOSIUM

MAY 14–16, 1992

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Chairmen
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Cedars-Sinai Medical Center
The Office of Continuing Medical Education
Room 2727
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Los Angeles, CA 90048

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BuSpar® (buspirone HCl)

References: 1. Feighner JP, Cohn JB. Analysis of individual symptoms in generalized anxiety—a pooled, multistudy, double-blind evaluation of buspirone. *Neuropsychobiology* 1989;21:124-130. **2.** Newton RE, Marunycz JD, Alderdice MT, Napoliello MJ. Review of the side-effect profile of buspirone. *Am J Med* 1986;80 (suppl 3B):17-21. **3.** Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82 (suppl 5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance.* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding, and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B. Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed unforward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular*: Tachycardia/palpitations 1%. *CNS*: Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT*: Blurred vision 2%. *Gastrointestinal*: Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal*: Musculoskeletal aches/pains 1%. *Neurological*: Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin*: Skin rash 1%. *Miscellaneous*: Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

MJL8-4270R2

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▲ Proven anxiolytic efficacy[1]

▲ Smooth, progressive action —relief starts within 1 week, progresses steadily through the fourth week of therapy[1]

▲ No more sedation (10%) than seen with placebo (9%)[2]

▲ Nonaddictive, no evidence of withdrawal syndrome[3]

▲ More commonly observed untoward events include dizziness (12%), nausea (8%), headache (6%), and nervousness (5%)

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(buspirone HCl)

Progressive Relief of Persistent Anxiety.

Please see references and brief summary on adjacent page.

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Articles

Disposable Products in the Hospital Waste Stream

DANIEL J. GILDEN, MD; KENNETH N. SCISSORS, MD; *and* JAMES B. REULER, MD; *Portland, Oregon*

Use of disposable products in hospitals continues to increase despite limited landfill space and dwindling natural resources. We analyzed the use and disposal patterns of disposable hospital products to identify means of reducing noninfectious, nonhazardous hospital waste. In a 385-bed private teaching hospital, the 20 disposable products of which the greatest amounts (by weight) were purchased, were identified, and total hospital waste was tabulated. Samples of trash from three areas were sorted and weighed, and potential waste reductions from recycling and substituting reusable items were calculated.

Business paper, trash liners, diapers, custom surgical packs, paper gowns, plastic suction bottles, and egg-crate pads were among the 20 top items and were analyzed individually. Data from sorted trash documented potential waste reductions through recycling and substitution of 78, 41, and 18 tonnes per year (1 tonne = 1,000 kg = 1.1 tons) from administration, the operating room, and adult wards, respectively (total hospital waste was 939 tonnes per year). We offer specific measures to substantially reduce nonhazardous hospital waste through substitution, minimization, and recycling of select disposable products.

(Gilden DJ, Scissors KN, Reuler JB: Disposable products in the hospital waste stream. West J Med 1992 Mar; 156:269-272)

During the last two decades, hospital reliance on disposable products has increased dramatically, with these items now accounting for as much as 85% of hospital medical equipment.[1] Inevitably, this produces an immense quantity of nonhazardous hospital waste.

The medical system's waste would be less important if landfill space were plentiful. Regional landfill space is so scarce, however, that lengthy transport of waste through environmentally sensitive areas is often required to reach available landfills. As a result, regional landfill disposal fees are increasing by as much as 400% per year,[2] and the disposal fees exceed the purchase price for some disposable products.[1] These financial and environmental liabilities of waste disposal make reducing the quantity of nonhazardous waste imperative.

To identify means of reducing quantities of nonhazardous hospital waste, we studied the use of disposable products and disposal patterns at Emanuel Hospital and Health Center (EHHC), a 385-bed private teaching hospital in urban Portland, Oregon. We found that through substitution, minimization, and recycling of select disposable products, profound reductions in waste production could be achieved. Based on our findings, specific recommendations are offered to guide hospitals in responsible waste management.

Study Design and Methods

This is an observational case study of the relationship between disposable products and waste excess in an urban teaching hospital.

The most commonly ordered disposable items were identified from purchasing cost data. Individual cases of the most common 150 items were weighed and then ranked by their yearly total weight. Like items of differing sizes were combined to give a single total for each category—for example, gloves of different sizes were weighed together.

We tabulated the total weekly output of EHHC's nonhazardous waste—the waste that is noninfectious, noncytotoxic, and nonradioactive.[3,4] The composition of this waste was determined by a detailed examination of trash from 3 of the hospital's 16 areas. Two of the authors (D. G. and K. S.) hand-sorted 10% of the daily waste from administration, the adult wards, and the operating room into three categories: reusable substitute available, recyclable, and trash. The first category was limited to those disposable items deemed to have safe, medically acceptable, and financially comparable reusable alternatives. Recyclable items were limited to white bond paper and computer paper to conform with the hospital recycling program. The sorted waste from each of the three hospital areas was then weighed, and the weight proportion for each category from each hospital area was calculated.

Errors for the weight proportion were calculated as the standard error of the proportion. Sampling was conducted at two separate sessions a month apart.

Results

The 20 disposable products of greatest yearly weight are ranked in Table 1.

In 1975, a 6-tonne load of compacted hospital waste was collected from EHHC weekly. Without a commensurate increase in hospital size, in 1991 a 6-tonne load was collected three times weekly, yielding 939 tonnes of waste annually. At 6.8 kg per hospital bed per day, EHHC's output of nonhazardous waste is consistent with previously published estimates.[4,5]

Each day, 460 variably filled 30-gallon plastic trash bags are collected from throughout the institution. The data on sorted waste from three hospital areas are given as weight proportions in Table 2. No infectious or hazardous material was found during the sorting process. By extrapolating from these weight proportions, the yearly reductions in trash resulting from reusable alternatives would be 10.5 tonnes from administration, 41 tonnes from the operating room, and 11.3

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TABLE 1.—*The Top 20 Disposable Items Purchased by Total Yearly Weight*

Item	*Weight, tonnes per year**
Business paper (8.5" × 11" and computer)	84.4†
Plastic trash liners	35.5
Paper towels	31.9
Food service (paper cups, paper plates, plastic knives)	31.8†
Gloves, nonsterile	27.3
Admission kits	19.2
Diapers (adult and infant)	15.2
Toilet paper	10.5
Plastic linen disposal liners	10.3
Orthopedic surgery packs	9.9
Surgical gowns	8.8
Underpads ("Chux")	7.4
1-Liter plastic suction bottles	5.8
Sterile cloth towels	5.3
Major laparotomy packs	5.3
Egg-crate pads	4.9
Obstetric delivery packs	4.3
Spinal fusion packs	3.0
"Sharps" wall-mount containers	2.9
Plastic surgery packs	2.7

*1 tonne = 1,000 kg = 1.1 ton.
†Purchasing records were not sufficiently detailed to determine the weight of all ordered products in these categories; thus, the actual weights are greater than those listed.

tonnes from the adult wards. The yearly reductions resulting from recycling would be 67.5 tonnes from administration and 6.5 tonnes from the wards. Substitution and recycling of select disposable products from these three hospital areas would reduce the yearly waste total at EHHC by 136.8 tonnes (15% of the hospital total). At a disposal fee of $78 per tonne, EHHC would save $10,670 yearly.

Discussion

In the process of collecting the data, we recognized three strategies to safely reduce the use of disposable products: substitution, minimization, and recycling. Specific examples from Table 1 are used in the following discussion in reference to these three strategies.

Substitution

The decision to use a particular disposable product is based largely on considerations of safety, convenience, and cost.[6] Bearing these factors in mind, we identified certain frequently used products for which acceptable reusable alternatives exist.

Infant diapers. At EHHC, the nursing personnel recently initiated a successful campaign to switch from disposable to cloth diapers. This substitution will remove 359,000 disposable infant diapers from the waste stream yearly (12.7 tonnes) and decrease hospital costs by approximately $30,000. At least ten other area hospitals have also converted to cloth infant diapers.

Of parents with infants, 90% use disposable infant diapers.[7] By using cloth diapers in the hospital, parents will be exposed to this environmentally and financially superior alternative.

Adult diapers. The elderly population is the fastest-growing segment of our society. A report by the Surgeon General estimates that the cost of diapering the incontinent elderly is

TABLE 2.—*Weight Proportion of Hand-sorted Nonhazardous Waste by Hospital Area*

Hospital Area	*Reusable Substitute Available* % ± SE†*	*Recyclable,* %*	*Trash, %*
Administration	7 ± 0.8	48 ± 10	45 ± 9.8
Medical and surgical wards	19 ± 6.3	11 ± 6.0	70 ± 6.4
Operating room	28 ± 6.1	0	72 ± 6.1

*See text for extrapolated yearly weights.
†SE = standard errors of the proportion (see text).

$8 billion per year,[8] which exceeds the combined national expenditure on dialysis and coronary artery bypass surgery.[9] Most incontinent adults use disposable diapers because acceptable cloth diapers have not been developed. For example, one local nursing home that uses 36,600 adult diapers per year (4.8 tonnes) switched from cloth to disposable diapers last year because of improved leakage control and convenience offered by the disposable product.

In 1990, 18,500 disposable adult diapers were used at EHHC (2.4 tonnes). The development of an adequate cloth product would reduce this growing contribution to the waste problem.

Custom disposable surgical packs. Custom disposable surgical packs have been used extensively over the last 10 years because they provide a high level of efficiency and convenience. The use of these packs, however, generates unnecessary waste from the disposal of unused items and items that have reusable alternatives. In examining the major laparotomy pack used at EHHC, we identified three items with reusable alternatives: large plastic basins, cloth towels, and plastic light handles. Metal basins can be substituted for the plastic basins in most instances. Reusable, high-grade cloth towels can be substituted for disposable, low-grade cloth towels, which are used extensively also as individual items. Metal handles that have been sterilized or covered with a disposable sterile cover can be substituted for disposable light handles. These substitutions would decrease the weight of each disposable laparotomy pack by 10%. If similar changes were made in all of the commonly used major surgical packs, there would be a decrease of about 3 tonnes of trash yearly at EHHC.

Although the effect is difficult to analyze fully, specific substitutions in the surgical packs may yield a net cost savings as well. The hospital pays $79 for each surgical pack. With the increasing reliance on capitated reimbursement plans, only a fraction of the $219 charge to the patient is collected. We estimate that the increased initial cost of these three reusable pack items would be compensated for after ten uses. Although reusable products impose the additional costs of sterilization, packaging, and replacement, these costs are in some measure counterbalanced by the savings from costs no longer associated with perpetual restocking and disposal of disposable products.

Disposable gowns. More than 8 tonnes of disposable gowns are used yearly at EHHC. Although a recent review stressed the importance of a truly impermeable barrier during procedures that pose a high risk for exposure to the human immunodeficiency and hepatitis viruses,[10] there are two strategies for avoiding overuse of disposable gowns. First, cloth gowns with a thin, reusable or disposable, imperme-

able liner would suffice during high-risk procedures. Second, a cloth gown alone can be used during low-risk procedures such as cystoscopy, angiography, and elective endoscopy.

Plastic suction bottles. In 1990, 22,600 disposable 1-liter hard plastic suction bottles were used at EHHC (5.8 tonnes). Recognizing the wastefulness of this practice, the operating room staff now uses disposable liners, similar to those used for wastebaskets, and reuses the containers. Hospitalwide use of the lighter liners would reduce waste by 3 tonnes yearly at EHHC. There is no significant cost difference between the plastic liners and the hard plastic containers.

Foam egg-crate pads. Foam egg-crate pads are used on beds to prevent pressure ulcerations and provide patient comfort. Foam pads do not reduce surface pressure below capillary filling levels over bony prominences, however, and thus they do not prevent or treat pressure ulcerations.[11,12] Because many comfortable specialized mattresses and mattress overlays are effective in preventing and healing pressure sores,[13] it makes more sense to provide a pressure-reducing mattress.

Preventing skin breakdown has economic as well as medical implications. Nosocomial pressure ulcers increase the nonreimbursed costs of a hospital stay. Over time, these costs would most likely exceed the purchase price of pressure-reducing mattresses. Based on this concept, hospitals of the Kaiser Permanente health maintenance organization in Portland will routinely use pressure-reducing mattresses on their medical and surgical wards.

At EHHC, this practice would eliminate disposal of 4,600 egg-crate pads yearly (4.9 tonnes). Although many of these pads go home with the patients, the pads ultimately find their way to landfills.

Suture removal kits. Single-use disposable instrument sets are used widely for suture removal and dressing changes. The set is packaged in a plastic tray and contains three poor-quality instruments, an alcohol swab, a povidone iodine swab, two cotton-tipped applicators, two gauze sponges, and—mysteriously—a safety pin.

An ingenious "stitch cutter" is now available that makes the instrument set obsolete for suture removal (Figure 1). This instrument is a simple piece of stainless steel with a razor-edged hook at one end designed to slip easily under and cut sutures. The disposable stitch cutter combined with a reusable forceps is an efficient replacement for the instrument set. Likewise, most dressing changes can be done with clean, reusable instruments and appropriate dressing material—again making the disposable instrument set unnecessary.

Figure 1.—A standard disposable suture removal set **(left)** is compared to a stitch cutter **(right)**.

In 1990, 7,500 instrument sets were used at EHHC. Substituting the 35-cent stitch cutter for the $6 instrument set would reduce the cost to the hospital by over $40,000 per year. Actual hospital savings would vary depending on reimbursement.

Even though the instrument set is not among the heaviest or most costly disposable items, it serves as an example of linked waste and cost reduction through thoughtful substitution.

Minimization

Waste reduction by minimizing disposable product use can be accomplished by three methods. First, using select singly packaged items, such as central venous catheters and guidewires, will avoid unnecessary squandering of an entire kit to obtain a single item. Second, employees can be educated in parsimonious use of common disposable products, such as food service items, gloves, and paper towels. Third, since waste begets waste, quantities of disposable packaging and trash can liners will decrease as the overall use of disposables decreases. As an illustration, reducing the use of trash can liners by 10% would reduce the yearly total waste at EHHC by 3.5 tonnes and reduce the yearly cost to the hospital by $6,000.

Recycling

Recycling is the method by which the greatest reductions in waste can be accomplished. The recycling program at EHHC includes white paper, computer paper—which together are the heaviest disposable products used in the hospital (Table 1)—and cardboard boxes. In addition to reducing waste, recycling saves money. Disposing of EHHC's 84.4 tonnes of paper costs $6,600 per year, while recycling that amount would yield $5,500 per year—a net savings of $12,100 per year. Further savings of approximately $100 per tonne could be achieved by recycling other products, such as newspaper, glass, aluminum, and cardboard.

Conclusion and Recommendations

Nonhazardous hospital waste is an important contributor to the national waste problem. Based on our study of waste production in a major hospital, we recommend that hospitals adopt the following measures:

- Substitute cloth diapers for disposable diapers in the pediatric areas. The practice of dispensing free samples of disposable diapers at discharge from the newborn nursery should be discontinued.
- Substitute reusable cloth gowns and towels for disposable ones whenever medically acceptable.
- Require each department to examine the contents of all disposable packs, trays, and kits with the goal of substituting reusable products for disposables whenever feasible and eliminating infrequently used items.
- Use lightweight disposable liners for 1-liter suction bottles.

- Substitute comfortable, permanent, pressure-reducing mattresses for egg-crate pads.
- For suture removal, substitute the "stitch cutter" and a reusable forceps for the disposable instrument set.
- Stock commonly contaminated individual items, such as guidewires and catheters, to avoid wasting an entire kit when these are needed singly.
- Reduce the use of all disposable products through employee education.
- Recycle white paper, computer paper, and cardboard boxes. Investigate the feasibility of recycling other materials, and implement a comprehensive recycling program, which would include preferential use of recycled products.
- Support research and development of improved reusable products, such as adult cloth diapers.
- Re-examine the economic effect of disposable products in light of fixed reimbursement rates and rapidly increasing disposal fees.
- Form a multidisciplinary institutional committee to address the issue of nonhazardous waste management.

We urge physicians, health care administrators, and all health care workers to make responsible decisions in the purchase and use of disposable products. In so doing, the medical system will lead the community in conserving natural resources and sparing limited landfill space.

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Management of Alcoholism in the Primary Care Setting

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Primary care physicians can play an important role in managing alcoholic patients. Identifying and treating alcoholism early, before it has interfered with patients' relationships and work, may increase the likelihood of prolonged recovery. Simple office interventions can help motivate patients to abstain and seek treatment. People who abuse alcohol and are unwilling to abstain can benefit from a recommendation to reduce their intake of alcohol. For alcohol-dependent patients who decide to stop drinking, primary care physicians often can manage withdrawal on an outpatient basis. Selecting an appropriate treatment program for each alcoholic patient is important, and referral to a specialist to assist in matching patients to treatments is often necessary. Primary care physicians also can help prevent relapse. Although disulfiram is of limited value, primary care physicians can support recovery by identifying coexistent psychosocial problems, helping patients to restructure their lives, and ensuring continuity of care.

(Bradley KA: Management of alcoholism in the primary care setting. West J Med 1992 Mar; 156:273-277)

This is the second of two articles on alcoholism in the primary care setting and focuses on the outpatient management of alcohol abuse and dependence, building on the discussions of screening and diagnosis found in the first article.[1] Unless otherwise stated, I again will rely on the definitions of alcohol abuse and dependence used in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R). In general, alcohol abuse entails continued drinking despite alcohol-related physical, social, or occupational problems or in hazardous situations, whereas alcohol dependence involves a greater disability caused by drinking, often with a history of tolerance and withdrawal. The management steps discussed in this article are summarized in Table 1.

From Diagnosis to Treatment—The Primary Care Physician's Role

Early Identification and Treatment

A patient's social situation at the time of treatment can have a substantial effect on the likelihood of recovery. Of men living with a spouse or employed on entering treatment, 45% and 31%, respectively, were abstinent at 8 years, compared with 21% of those in a "skid row" setting.[2] Thus, by identifying and treating alcohol abuse early, before it has interfered with patients' jobs and relationships, physicians may improve their patients' chances for recovery.

Motivating Patients

Patient motivation appears to be a key ingredient in successful recovery from alcoholism and one that can be influenced by primary care physicians. Measures that increase patients' perceptions of the risk of drinking, especially information regarding the severity of their drinking-related problems, have been shown to significantly improve patient motivation to abstain.[3,4] For instance, presenting—in a supportive, nonconfrontational manner—the risk and realities of cirrhosis to an alcoholic person with abnormal liver function test results might motivate that patient to seek treatment. Several studies have shown that clear advice and follow-up, particularly after discussion of the serious nature of the problem, also increase patient motivation and consequent behavior change.[3-7] When patients miss appointments, letters or phone calls from their physicians have a notable effect on motivation to return and comply with treatment recommendations.[3] Finally, because waiting to begin alcoholism treatment apparently decreases motivation, primary care physicians probably can improve treatment results by facilitating rapid entry into treatment once a patient is willing.[3]

Substantial research also suggests that physician empathy plays an important role in patient motivation and treatment results. In contrast, confrontive behaviors have been found to

TABLE 1.—*Primary Care Provider's Role in Managing Patients With Alcoholism*

- Identify and treat alcoholism as early as possible
- Increase patient motivation with specific feedback about the problem, clear advice to abstain, close and persistent follow-up, and an empathic attitude
- Advise alcohol-abusing patients unwilling to abstain to at least reduce their alcohol intake
- Prescribe benzodiazepines and evaluate patients daily when withdrawal is present
- Match patients to appropriate treatment programs, often in consultation with specialists
- Occasionally, prescribe disulfiram to promote abstinence in appropriate patients
- Identify and manage coexistent psychosocial problems
- Advise patients to participate in Alcoholics Anonymous or other relapse prevention programs following treatment
- Encourage patients to restructure their lives by developing new habits, new social supports, and new community involvements
- Ensure continuity of care by scheduling regular follow-up visits, contacting patients after missed appointments, and being receptive and supportive toward relapsed patients

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ABBREVIATIONS USED IN TEXT

AA = Alcoholics Anonymous
DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised

increase patient resistance and their drinking.[3,4] Thus, it seems likely that primary care physicians can influence alcoholic patients' motivation to abstain simply by displaying such qualities as respect, caring, understanding, and an active desire to help.[3]

Controlled Drinking Versus Abstinence

The available evidence suggests that alcohol-dependent patients rarely, if ever, revert to normal drinking, although there has been considerable controversy in this area. In the 1970s Sobell and Sobell claimed that alcohol-dependent patients could successfully learn and maintain controlled drinking, but their work was discredited by a careful review of their patients and study results.[8] Several reports by the Rand Corporation claimed to document nonproblem drinking in alcoholic persons, but those with alcohol dependence at any time in the study were likely to have continued drinking problems.[9] Likewise, Vaillant found that once patients had been dependent on alcohol, they were unlikely to control their drinking without abstinence.[10] Abstinence should therefore be the cornerstone of any management strategy for alcohol-dependent patients.

Some patients who abuse alcohol, on the other hand, appear able to return to nonproblem drinking. Vaillant found that, over eight years, almost half of the alcoholic persons he studied reverted to social drinking, while only a third became dependent on alcohol. Likewise, the patients in the Rand studies who reverted to controlled drinking were usually nondependent problem drinkers. Vaillant's work and the Rand studies preceded the DSM-III definitions of alcohol abuse and dependence, but their definitions were similar enough that it is reasonable to assume some overlap between their patients and those who meet DSM-III-R criteria for alcohol abuse.[11] Thus, while the proportion of alcohol-abusing patients who return to social drinking can be debated, the fact that some do is difficult to dispute.

Given this evidence, how should we manage alcohol abuse in general medical practice? The standard of care is that the management of all alcohol abuse, like dependence, should be founded on abstention. This is the best approach because abstinence is the safest way to avoid both the physical, social, and occupational costs of alcohol abuse and the risk of progression to dependence.

Many patients will not be willing to stop drinking or enter treatment when first presented with a diagnosis of alcohol abuse, however, and these patients should be advised to cut down. There are several possible benefits of advising controlled drinking in this population. A recommendation for controlled drinking—no more than two drinks a day—can serve as a diagnostic strategy. In patients unable to control their intake, a trial of controlled drinking may overcome denial about an alcohol problem, and subsequently some patients may be willing to abstain and enter treatment.[12] In patients who are able to control their intake, decreasing the amount they drink can decrease morbidity. A British study found that after general practitioners recommended controlled drinking, the quantity of alcohol consumed by "excessive drinkers" (over 35 drinks a week for men) decreased significantly and was reflected in significant decreases in blood pressure and aspartate aminotransferase (AST, formerly SGOT) at 12 months.[5] In addition to the possible medical benefits of controlled drinking, discussions of a patient's successes and failures can help maintain an open dialogue and a therapeutic relationship between the physician and the patient, allowing physicians to continue to urge abstinence as additional alcohol-related problems arise.

For these reasons, I think that after firmly recommending abstinence and after a frank discussion with patients about the serious risks of continued drinking, alcohol-abusing patients who refuse to stop drinking should be advised to reduce their intake. This approach is not recommended for patients who are alcohol-dependent, because it is unlikely that they would be able to control the amount they drink.

Many alcohol treatment specialists and persons affiliated with Alcoholics Anonymous (AA) will strongly disagree with any management approach that includes controlled drinking.[10,13] It should be stressed that I am not recommending such a strategy as the preferred treatment, but rather as a second choice with potential therapeutic benefits. This circumstance seems analogous to one where a patient with a life-threatening infection refuses to stay in the hospital. Although the recommended treatment is intravenous antibiotics, when the patient leaves against medical advice most physicians would, as the best possible substitute, prescribe oral antibiotics and arrange follow-up. In this spirit, primary care physicians should recommend controlled drinking to patients who abuse, and refuse to abstain from, alcohol.

Inpatient Versus Outpatient Detoxification

Historically, detoxification involved withdrawal from alcohol in an inpatient setting, making a hospital stay the first step of rehabilitation. A randomized, controlled study of 164 patients with mild-to-moderate withdrawal symptoms and no active medical or psychological problems found outpatient detoxification to be safe and effective.[14] Outpatient detoxification included daily visits to the clinic where patients were evaluated for withdrawal symptoms and placed on benzodiazepine therapy over three to five days. Both inpatients and outpatients were referred to AA for long-term rehabilitation. Despite the fact that many participants had unstable social situations, there were no complications of outpatient withdrawal. Furthermore, in spite of a higher attrition rate among outpatients, both settings appeared equally effective with respect to abstinence, sobriety, alcohol-related problems, recurrent need for detoxification, and entry into long-term rehabilitation at six months. Inpatient detoxification was 9 to 20 times more expensive, including lost opportunity costs.[14]

Although the study may have been biased by minor differences in the two randomly selected groups and lacked the power to detect small differences in results, the findings—large differences in cost and a lack of any differences in outpatient complications or results—support outpatient management of mild to moderate alcohol withdrawal. Such patients should be seen daily by the physician or a surrogate and evaluated for withdrawal symptoms to be treated with benzodiazepine therapy. Inpatient detoxification remains appropriate, however, when withdrawal is complicated by seizures or other medical or psychiatric problems, and perhaps when a patient has failed previous outpatient detoxification or requests inpatient management.

The Role of Medications in Detoxification

Although it has been suggested that alcoholic persons can safely withdraw without medication,[15] evidence in animals and humans suggests that untreated withdrawal may predispose patients to withdrawal seizures and cognitive defects.[16] Therefore, benzodiazepines should be considered for all withdrawing patients. Although opinions differ regarding the benefits of short- or long-acting benzodiazepines, the short-acting varieties (oxazepam or lorazepam) are metabolized primarily by glucuronidation and may be safer for the elderly and for patients with liver disease. If diazepam is used, a starting dose of 10 to 20 mg with repeated doses of 5 mg every four to six hours as needed to control symptoms can be prescribed the first day, decreasing the total daily dose by half each day thereafter.[17]

β-Blockers, which mask the sympathetic discharge of withdrawal, have been shown to speed the return to normal of vital signs, substantially decrease the length of hospital stay, and decrease benzodiazepine requirements.[18] Although a recent inpatient trial reported no complications from treatment with atenolol,[18] there have been previous reports of increased delirium tremens in withdrawing patients treated with propranolol.[19] Therefore, until further data have accumulated, β-blockers are probably best reserved for the inpatient setting where patients can be monitored closely. Even in these patients, β-blockers probably should be used as an adjunct to, not instead of, benzodiazepines because of the possible sequelae of untreated withdrawal mentioned previously.

Treatment Programs

Studies of alcoholism treatment programs have been plagued by multiple definitions of alcoholism, heterogeneous treatment populations, bias because of self-referral, the relapsing and remitting nature of the disease, attrition, and a short duration of follow-up. Nevertheless, some general conclusions about treatment can be made.

No single alcoholism treatment—behavioral, psychotherapeutic, aversion, pharmacologic, or self-help—has well-documented short- or long-term benefits for all patients. Likewise, the intensity (residential versus nonresidential) and duration of treatment have not been shown to alter patients' outcomes in controlled studies.[4] Moreover, studies of pooled data, comparing treatment to no treatment, have been unable to show clear-cut treatment benefits.[9,10,20-22] Nevertheless, an extensive review of the literature by a subcommittee of the Institutes of Medicine concluded that "a variety of specific treatment methods have been associated with increased improvement, relative to no treatment or alternative treatments, in controlled studies."[4] Additionally, there is evidence that alcoholism treatment programs have overall cost benefits to society.[21,23] For these reasons, primary care physicians are advised to refer alcohol-abusing and alcohol-dependent patients for treatment.

Selecting a Treatment Program

Matching patients to the individual treatments that are most likely to prove successful for them is a challenge. Demographic variables (such as age, sex, and marital status), psychological factors (such as psychiatric diagnoses, self-image, and locus of control), severity of alcoholism, and antecedents to drinking have all been found to affect the results of specific patient-treatment matches.[24] For example, patients who are socially unstable (for example, homeless or unemployed) or those with severe alcohol dependence or coexistent psychopathology may have more success in residential programs, whereas socially stable persons appear to do well in less costly nonresidential treatment settings.[4]

Data on matching alcoholic patients to treatment programs are incomplete at this time, and there are no easily accessible guidelines for use by primary care physicians, although both issues are being addressed by the Institutes of Medicine.[24] In the meantime, clinicians can refer patients to specialists—social workers, alcoholism counselors, or mental health professionals with knowledge of alcoholism treatment resources—to be evaluated and matched to a suitable treatment option. In some localities publicly supported matching programs are available, and ideally more will be evolving.[24] The National Council of Alcoholism has offices in many cities and can also assist in such matching.

Alcoholics Anonymous

One of the most accessible and widely recommended treatment programs is AA. Begun by two alcoholic persons, AA is a network of self-help groups offering free, daily meetings. In AA meetings alcoholic persons are guided by others recovering from alcoholism through 12 suggested steps. These steps have been described as a "quasireligious expression of the process of change seen in psychotherapy, . . . [involving] accepting the diagnosis . . . , believing that recovery is possible, undergoing a period of self-exploration, and finally translating this self-knowledge into appropriate interpersonal behavior."[25]

Despite extensive anecdotal reports of the value of AA, there are only three controlled studies of its effectiveness, and the results have been mixed.[4] Nevertheless, the fact that AA is remarkably successful at attracting alcoholic persons to recovery, is free, and appears to be effective for relapse prevention make it an important resource for primary care physicians and their patients.[4]

Alcoholics Anonymous groups differ, each with a character of its own. Some are open to the public, others are closed. Once patients agree to attend, having them call for information from the physician's office will ensure that the referral is completed. Patients should be encouraged to try several open meetings and return to discuss their impressions with the referring physician before deciding "it's not for them."[25]

Relapse Prevention

The Role of Drugs in Abstinence

Disulfiram (Antabuse) has a limited role in maintaining abstinence. It allows alcohol-abusing patients to make the decision not to drink once a day, postponing impulses to drink five to seven days, and has been shown to reduce the frequency of alcohol consumption over the short run. In a 1989 position paper, the American College of Physicians stated that *supervised* administration of disulfiram is probably effective in voluntary treatment of outpatients and compulsory treatment for violent or criminal patients, and that *self-administration* of disulfiram was possibly effective, especially in motivated, older, socially stable alcoholic persons.[26] Another study, however, found no benefit of disulfiram with respect to total abstinence, time to first drink, employment, or social stability over one year, although patients treated with disulfiram did have fewer drinking days.[27]

The alcohol-disulfiram reaction is usually mild, including flushing, headache, nausea, and vomiting, beginning

about 5 minutes after ingestion and lasting 30 to 180 minutes. The potential complications of the drug are many (Table 2).[28-30] Occasional severe reactions have included myocardial infarction, congestive heart failure, arrhythmia, seizure, and death.[29] These more severe reactions usually occur at doses of at least 500 mg per day after multiple drinks and may be associated with concurrent use of sympatholytic or psychotropic drugs.[30] Any ethanol-containing medication or substance (including 15 ml of over-the-counter cough syrup, cutaneously applied rubbing alcohol, and paraldehyde) can cause a reaction.[29,31]

Because of disulfiram's teratogenic effects, pregnancy is an absolute contraindication to its use. Relative contraindications include cardiac or metabolic diseases; pulmonary, hepatic, or renal insufficiency; neuropathy, organic mental disorders, depression, personality disorders, psychosis, or concurrent administration of sympatholytic or psychotropic medications.[29-31]

Patients who are started on disulfiram therapy must be educated about the risks of drinking, of taking other medications, possible side effects, and the fact that pregnancy is absolutely contraindicated. Disulfiram should be started at 250 mg per day, and administration should be supervised if possible. Patients should carry identification stating that they are taking the drug. Under no circumstances should the disulfiram-alcohol reaction be provoked deliberately, as was previously recommended as a form of aversion therapy. Trials with disulfiram implants have shown erratic blood levels; implants are not currently recommended.[4]

Lithium, which had been shown in early studies to prolong abstinence, was no better than placebo in a recent Veterans Administration cooperative study of depressed and nondepressed alcoholic patients.[32] It has no place in the treatment of chronic alcoholism. No other drugs currently available in the United States are of proven use in promoting abstinence.[4]

Managing Coexistent Psychosocial Problems

Coexistent psychiatric illness often predisposes patients to relapse,[33] and primary care physicians can help identify and treat it. Untreated depression has a documented adverse effect on outcome in alcoholic men,[34] and treating depression that persists after a patient is sober might help maintain remission.[4] Therefore, if depression lasts beyond the early weeks of abstinence, a primary care physician should consider initiating specific antidepressant therapy with either medication or referral for psychotherapy. Similarly, stress management training may help maintain abstinence, especially in patients with coexisting anxiety.[4]

Social and family problems are also thought to contribute to relapse, and there is evidence that specific interventions aimed at these problems improve long-term results. For instance, behavioral marital therapy has been shown to decrease treatment dropout and relapse rates, while social skills training appears to improve results in alcoholic persons lacking these skills.[4] By being alert for concomitant social problems, primary care physicians can refer recovering alcoholic patients for specialized assistance when indicated.

Restructuring Patients' Lives

Vaillant has identified four conditions that contribute to stable abstinence after treatment: a substitute nonchemical dependency, new social supports, inspirational group membership, and compulsory treatment.[2] He hypothesizes that these conditions help impose structure on recovering alcoholic patients' lives, thereby interfering with any tendency to drink.[2] According to Vaillant, AA often fulfills three of these conditions. Attending AA meetings may serve as a substitute addiction; other AA members offer new social support; and the group's philosophy, reflected in the 12 steps, provides spiritual support.[2] Additionally, such conditions are often incorporated into aftercare programs aimed at preventing relapse.

For patients unwilling to attend AA meetings or other aftercare programs, primary care physicians can use Vaillant's findings to help patients remain sober. Specifically, a regular schedule of follow-up appointments, perhaps accompanied by a calendar with each date marked, might mimic some of the effects of compulsory treatment programs. Such structured follow-up has been shown independently to improve abstinence rates.[4] Advising patients to develop new exercise programs, hobbies, or other routines might foster nonchemical dependencies, which supports abstinence. Encouraging patients to join a religious or other community organization might lead to new social supports and provide inspirational group membership.

Continuity of Care

Alcoholism is a chronic relapsing and remitting disease, and, despite the best of intentions, most recovering alcoholic persons experience at least one relapse. While eventually paraprofessional caseworkers might provide continuity of care for these patients,[35] primary care physicians can help fill this important niche.

Primary care physicians can build a foundation for continuity of care by discussing the relapsing nature of the disease openly with recovering alcoholic patients. The frank discussion of relapse as a feature of the disease can help decrease a patient's sense of personal failure when relapse occurs. Moreover, the explicit articulation of a physician's willingness and expectation to care for a patient with alcoholism, if

TABLE 2.—*Possible Complications of Disulfiram Therapy**

Side Effects	
Fatigue and sedation	Gastrointestinal upset
Dermatitis	Hypertension
Impotence	Increased liver function test results and cholesterol level
Depression and psychosis	
Body odor and halitosis	
Toxicity	
Peripheral neuropathy, optic neuritis, and polyneuritis	
Fulminant or cholestatic hepatitis	
Drug Interactions	
Increases the half-life of phenytoin and coumadin	
Potentiates metronidazole and isoniazid, including possible neurotoxicity and hepatic toxicity	
When taken with sympatholytics or monoamine oxidase inhibitors, may cause severe hypotension	
Results of Overdose	
Alone—primarily nervous system dysfunction	
With alcohol—tachycardia, hypotension, arrhythmia, myocardial infarction, stroke, and death	
Teratogenic Effects	
Primarily limb abnormalities	

*From *Physicians' Desk Reference*,[28] Barnes,[29] and Sellers et al.[30]

and when a relapse occurs, might encourage the patient to contact the primary care physician at such times, rather than seeking care elsewhere because of shame or guilt.

There are several potential benefits of such continuity of care. As discussed earlier, follow-up with an empathic physician can increase motivation for abstinence. In addition, an actively drinking patient would benefit by encountering a respectful physician familiar with that patient's previous desire and effort to abstain. The primary care physician might help motivate the patient to again abstain by asking about the events leading up to recurrent drinking and expressing optimism about the patient's ability to stop drinking again. The physician also could prescribe benzodiazepine therapy if needed to treat withdrawal. Frequent follow-up would help structure a patient's early days of sobriety. In contrast, relapsed alcoholic patients who seek treatment for trauma, withdrawal, or medical conditions in acute care settings are more likely to encounter a hostile environment in which the management of their primary problem, alcoholism, may not be addressed.[36]

Conclusion

Primary care physicians can play an important role in managing alcoholism. Alcohol-abusing patients can be identified early, before they become socially isolated or unemployed, perhaps improving their prognosis. Several simple interventions, easily incorporated into brief medical visits, can increase patient motivation, a key determinant of the results of treatment of alcoholism. Alcohol-abusing patients who are unwilling to abstain can be advised to limit their drinking, thereby decreasing morbidity while overcoming denial about their alcohol problem.

Once patients decide to abstain, detoxification, if necessary, can often be supervised safely in an outpatient setting. Matching these patients to an appropriate treatment program and maintaining close follow-up improve the likelihood of subsequent recovery, especially if attention is focused on relapse prevention. Perhaps most important to the successful management of alcoholism in the primary care setting, however, is the intrinsic benefit of a respectful, empathic, and ongoing relationship between an optimistic physician and an alcoholic patient.

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Articles

Effects of a Major Earthquake on Calls to Regional Poison Control Centers

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We retrospectively evaluated the effect of the Loma Prieta earthquake on calls to 2 designated regional poison control centers (San Francisco and Santa Clara) in the area. In the immediate 12 hours after the earthquake, there was an initial drop (31%) in call volume, related to telephone system overload and other technical problems. Calls from Bay Area counties outside of San Francisco and Santa Clara decreased more dramatically than those from within the host counties where the poison control centers are located. In the next 2 days, each poison control center then handled a 27% increase in call volume. Requests for information regarding safety of water supplies and other environmental concerns were significantly increased. The number of cases of actual poisoning exposure decreased, particularly poison and drug ingestions in children. Most calls directly related to the earthquake included spills and leaks of hazardous materials and questions about water and food safety. Regional poison control centers play an essential role in the emergency medical response to major disasters and are critically dependent on an operational telephone system.

(Nathan AR, Olson KR, Everson GW, Kearney TE, Blanc PD: Effects of a major earthquake on calls to regional poison control centers. West J Med 1992 Mar; 156:278-280)

On October 17, 1989, at 5:04 PM, the Loma Prieta earthquake, registering 7.1 on the Richter scale, struck northern California, resulting in 63 deaths, substantial injuries, and massive destruction of property.[1-3] During the initial 24 hours after the earthquake, there was significant disruption of telephone communications due to both physical damage and overloaded telephone circuits. Poison control centers are integral parts of emergency medical services, and it is imperative that they continue to function normally during a natural disaster. Like other emergency hotlines, however, they are entirely dependent on a properly functioning telephone service.

The San Francisco Bay Area Regional Poison Control Center (SFPCC) and the Santa Clara Valley Medical Center Regional Poison Control Center (SCPCC) are designated by the Emergency Medical Services Authority of the State of California to serve the two regions hit hardest by the Loma Prieta earthquake. This study was conducted to determine if the number and nature of calls to these two poison control centers changed as a result of the earthquake.

Methods

We retrospectively reviewed the records from the SFPCC and SCPCC for a 55-hour time period beginning immediately after the earthquake (5 PM Tuesday, October 17, to midnight Thursday, October 19, 1989). Records were also reviewed for a "control" 55-hour time period (5 PM Tuesday, October 10, to midnight Thursday, October 12, 1989) exactly one week before the earthquake. The use of call data from exactly one week before the incident was intended to minimize bias due to seasonal, daily, and hourly fluctuations in call volume.

Case data were extracted directly from written case records completed at the time of the call by the on-duty poison control center specialist. Variables extracted were date and time of call, call type (exposure or information), reason for exposure, county of caller, age and sex of patient, substance involved, route of exposure, and medical outcome. The definitions and criteria for selecting these variables were based on guidelines set by the American Association of Poison Control Centers (AAPCC).[4] In addition, the substance or topic of the call was categorized retrospectively into one of several subject categories—for example, water safety, food safety, drugs, household products, pesticides. At the SFPCC, additional data were obtained from a review of short case logs used for minor calls involving a request for information only (these abbreviated logs include only the following information: date, time, county, and subject of question).

The data were analyzed as a whole (information and exposure calls combined) and then separately for exposure calls only. By AAPCC definition, "exposure" calls are those in which an actual exposure—by ingestion, inhalation, skin contact, or other route—took place.

The number of calls in the first 12 hours after the earthquake ("early") was compared with a matching 12-hour control period and with that recorded in the remaining 43-

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ABBREVIATIONS USED IN TEXT

AAPCC = American Association of Poison Control Centers
SCPCC = Santa Clara Valley Medical Center Regional Poison Control Center
SFPCC = San Francisco Bay Area Regional Poison Control Center

hour postearthquake period ("late"). The mean call volumes were calculated for the entire month of October. The extracted data were entered into a computerized data base and analyzed using a standard statistical package (SAS). The differences in frequency between the control pre-earthquake and postearthquake periods call variables were tested for significance using either χ^2 or Fisher's exact tests.

Results

A total of 698 calls were received by the two regional poison control centers in the 55-hour period following the earthquake, as compared with 592 calls in the control 55-hour period a week earlier (Table 1). This difference represents an 18% increase in call volume. When broken down by "early" calls during the 12 hours immediately after the earthquake and "late" calls during the remaining 43 hours, a differing pattern emerged. The call volume was substantially reduced (31%) during the first 12 hours after the earthquake compared with baseline. In contrast, there was a sharp increase (27%) during the late postquake period compared with baseline. This pattern was noted for both participating poison control centers.

Immediately after the earthquake, there was a tremendous increase in the number of telephone calls to and from the Bay Area, resulting in electronic gridlock. The telephone system in northern California responded by sharply limiting incoming calls to affected areas while allowing outgoing calls (James Gleason, Pacific Bell, oral communication, December 1989). To ascertain whether a decrease in call volume immediately after the earthquake was due to limited telephone access to San Francisco and San Jose by callers outside the primary service county of each poison control center, we compared case referrals by county of origin. Calls originating from within San Francisco and Santa Clara counties fell from 25 calls to 21 (16% decrease) in the initial 12-hour period. In comparison, calls from outside these counties fell from 70 calls to 45 (36% decrease). Although the changes in call volume were not statistically significant, they suggest that callers outside of San Francisco and San Jose had greater difficulty reaching the poison control centers. The decreased call volume during the first 12 hours was not experienced by the Los Angeles Regional Poison Control Center, which is not in the geographic area affected by the earthquake (Michael Wieland, PharmD, Los Angeles County Medical Association Regional Poison Control Center, oral communication, October 1991).

Table 2 describes informational (nonexposure) calls by subject. The 207 information calls after the earthquake represent a 125% increase over baseline and account for all of the excess call volume (information and exposure) noted. Three specific subjects accounted for the majority of calls: food, water, and environmental safety. For information calls relating to water and environmental safety, the increases were statistically significant.

As shown in Table 3, exposure-related cases actually decreased by 4% overall in the postearthquake period. Nonetheless, there were significant proportional increases in the number of adult compared with pediatric cases and in those involving men compared with women. The number of calls involving ingestion and related to the misuse of a drug or

TABLE 1.—*Frequency of Poison Center Calls After the Earthquake Compared With a Control Pre-earthquake Period*

Time Period, h	Poison Center Calls: Pre-earthquake Control, No.	Poison Center Calls: After Earthquake, No.	Change, %
Initial 12*	95	66	−31
Subsequent 43	497	632	+27
Total 55-h observation period	592	698	+18

*$P < .05$, initial calls compared with subsequent calls.

TABLE 2.—*Information Calls Before and After the Earthquake*

Subject of Information	Control, No. (%)	After Earthquake, No. (%)
Water safety*	0 (0)	29 (14)
Food safety	7 (8)	32 (15)
Corrosives	2 (2)	4 (2)
Hydrocarbons	4 (4)	5 (2)
Environmental safety*	2 (2)	20 (10)
Plants	4 (4)	6 (3)
Pesticides	12 (13)	14 (7)
Other	61 (66)	97 (47)
Total information calls	92 (99)	207 (100)

*$P<.05$, as compared with all other information calls.

TABLE 3.—*Poison Exposure Calls After the Earthquake*

Variables	Control, No. (%)	After Earthquake, No. (%)
Total exposure calls	494 (100)	474 (100)
Demographics		
Adult (age > 18 yr)*	151 (31)	185 (41)
Male*	229 (49)	253 (56)
Reason for exposure		
Accidental, general	405 (82)	394 (83)
Misuse*	32 (6)	11 (2)
Suicide	21 (4)	27 (6)
Occupational	11 (2)	18 (4)
Abuse	5 (1)	3 (1)
Environmental	8 (2)	11 (2)
Other or unknown	12 (2)	10 (2)
Route(s) of exposure†		
Ingestion*	390 (79)	344 (73)
Inhalation	43 (9)	54 (11)
Dermal	30 (6)	30 (6)
Ocular	27 (5)	28 (6)
Bite or sting	11 (2)	17 (4)
Other or unknown	11 (2)	11 (2)
Medical Outcome		
No effect	195 (39)	170 (36)
Minor effect	109 (22)	116 (24)
Moderate or severe effect	20 (4)	19 (4)
Unrelated effect	14 (3)	20 (4)
Unknown or nontoxic exposure	112 (23)	114 (24)
Unknown or potentially toxic	41 (8)	31 (7)
Admitted to hospital	26 (6)	19 (4)

*$P<.05$.
†Total may exceed 100% because more than 1 route of exposure occurred in some patients.

TABLE 4.—*Subject of 48 Calls to SFPCC Assessed as Being Clearly Related to Earthquake*

Subject	*SFPCC Calls, No. (%)*
Hazardous materials*	12 (25)
Water safety	11 (23)
Food safety	8 (17)
Natural gas	5 (10)
Drugs	5 (10)
Household products†	4 (8)
Other or unknown	3 (6)

SFPCC = San Francisco Bay Area Regional Poison Control Center

*Hazardous materials included ammonia, liquid mercury, gasoline, leaking transformers, sodium cyanide, smoke, hydrofluoric acid, carbon monoxide, hydrochloric acid, and asbestos.

†Household products included mothballs, mercury thermometer, ant poison, and fiberglass.

product decreased significantly. Although not statistically significant, there were more calls regarding inhalation exposure, occupational exposure, environmental exposure, and suicidal overdose. There was a substantial decrease in the number of exposures related to drug abuse. There was no significant change in severity of medical outcome or the admission rate to hospital (Table 3).

Of the 455 calls to the SFPCC in the 55-hour postearthquake period, 48 were determined on reviewing the records to be clearly related to structural damage during the earthquake (Table 4). Besides questions about food and water safety, the calls included exposures to a variety of chemicals and other hazardous materials, such as broken asbestos and fiberglass insulation, spilled mercury, broken chemical containers (containing cyanide, ammonia, and hydrochloric acid); leaking transformers; natural gas from broken gas lines; smoke inhalation from fires; and a case of serious carbon monoxide poisoning from a portable generator used because the electricity was out. One caller had been siphoning gasoline just as the earthquake occurred and accidentally swallowed some.

Discussion

The immediate decrease in call volume to local poison control centers during the first 12 hours after the Loma Prieta earthquake was in large part caused by technical problems in the local telephone system. Existing circuits rapidly became overloaded by the huge volume of incoming calls to check on relatives or other loved ones. This hypothesis is supported by the finding that the call volume from within each host county remained relatively unchanged during this initial period, while calls from outside each host county decreased (although the fall in call volume was not statistically significant). After relatively normal telephone service resumed, the call volume from all served areas increased. Fortunately, the disruption of telephone service was relatively short and was not total, as might have occurred with an earthquake of greater magnitude.

There was a substantial decrease in the number of pediatric exposures, perhaps because many families remained home from work during the first few days after the earthquake and were likely to be watching their children more closely. Alternatively, parents might have failed to recognize some exposures because they were distracted by the events and disruptions associated with the earthquake. The increased number of exposures in adults and in men may reflect their greater involvement in clean-up or rescue efforts, although this was not analyzed. Clean-up and rescue operations may also explain the slightly increased volume of inhalation exposure. Although the increase in the number of work-related exposures was not statistically significant, it should be noted that probably fewer people were at work immediately after the earthquake.

More than a third of the 48 calls to the SFPCC judged as directly related to the earthquake involved hazardous materials and natural gas leaks. (Earlier hazardous materials disasters not associated with an earthquake had already highlighted the importance for poison control centers of maintaining specialized information resources and protocols for managing these incidents. For example, after a fire involving polychlorinated biphenyls in 1983, the SFPCC received more than 1,000 calls relating to the incident.) Most of the other earthquake-related calls involved questions of water and food safety, although there were no documented cases of poisoning from contaminated water or food. Even though food and water contamination is usually considered a problem for specialists in infectious disease or public health, poison control centers frequently handle such questions.

Summary

After a major earthquake affecting the San Francisco Bay Area, the poison control centers serving the region experienced an initial drop in call volume related to telephone system overload and other technical problems. In the next two days, however, each center handled a marked increase in call volume. Most of the calls directly related to the earthquake involved hazardous materials and questions about water and food safety. Regional poison control centers play an essential role in the emergency medical response to major disasters and are critically dependent on an operational telephone system.

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Conferences and Reviews

Blood-Brain Barrier and New Approaches to Brain Drug Delivery

Moderator
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Discussants
RUBEN J. BOADO, PhD; KEITH L. BLACK, MD; *and* PASQUALE A. CANCILLA, MD

This is an edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is Anthony T. Campagnoni, PhD, Professor of Psychiatry and Biobehavioral Sciences.

Morbidity caused by brain dysfunction affects more than 50 million persons in the United States. Although new neuropharmaceuticals have the potential for treating specific brain diseases, they may not effectively enter brain from blood. Safe strategies are needed for drug delivery through the brain capillary wall, which makes up the blood-brain barrier in vivo. Two of these strategies are reviewed, as are related new developments in the molecular and cell biology of the brain capillary endothelium. The production of chimeric peptides represents a physiologic-based strategy for drug delivery. It entails the covalent coupling of the neuropharmaceutical to a brain transport vector, allowing transportation through the blood-brain barrier. Another strategy is biochemical opening of the blood-brain barrier: intracarotid leukotriene infusion is a method for selectively increasing blood-brain barrier permeability in brain tumors without affecting barrier permeability in normal brain tissue.

(Pardridge WM, Boado RJ, Black KL, Cancilla PA: Blood-brain barrier and new approaches to brain drug delivery. West J Med 1992 Mar; 156:281-286)

WILLIAM M. PARDRIDGE, MD*: The morbidity of cancer and heart disease is dwarfed by illness caused by disorders of the brain, which affect 50 to 100 million persons in the United States (Table 1). The number of disorders of the brain commonly seen in the practice of internal medicine may be expanded even further because such problems as peptic ulcer, hypertension, or irritable bowel syndrome may be amenable to treatment by direct drug action on the brain.[1] In the 1990s, the Decade of the Brain, the traditional trial and error approach to drug development and design is giving way to rational drug design based on three-dimensional models of receptor structure. For example, new drugs for treating depression, stroke, Alzheimer's disease, fever, or anxiety may include corticotrophin-releasing hormone antagonists, calcitonin gene-related peptide agonists, amyloid protease inhibitors, α-melanocyte-stimulating hormone agonists, or cholecystokinin receptor antagonists, respectively.[1] In future, the driving force of drug design may be the expanding base of neuropeptide receptor biology that has emerged from research.

Unfortunately, drugs developed from rational drug design based on considerations of receptor biology may not be effective neuropharmaceuticals if these drugs are not transportable across the brain capillary wall, which makes up the blood-brain barrier in vivo. For example, the first product of recombinant DNA technology that may be used for treating a neurologic disease is nerve growth factor for treating Alzheimer's disease.[2] Nerve growth factor is a large protein of approximately 25,000 molecular weight and is not known to cross the blood-brain barrier.[3] Although proposals have been made to administer nerve growth factor through intraventricular drug delivery,[4] this approach requires a neurosurgical procedure. Moreover, the two caveats of intraventricular drug delivery are: the drug is distributed only to the surface of the brain and not deep into brain parenchyma,[5] and the drug is readily distributed into the peripheral circulation owing to rapid efflux of drug from the ventricular cerebrospinal

TABLE 1.—*Common Brain Disorders in the United States**

Disorder	*No. of Affected Persons, in millions*
Migraine headache	25
Alcohol abuse	25
Anxiety or phobia	25
Sleep disorders	20
Depression or mania	12
Drug abuse	10
Obsessive-compulsive disorder	4
Alzheimer's disease	3
Schizophrenia	2
Stroke	2
Epilepsy	2
Human immunodeficiency virus infection	1.5
Parkinson's disease	.5

*From Pardridge.[1]

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ABBREVIATIONS USED IN TEXT

cDNA = complementary DNA
mRNA = messenger RNA
p^I = isoelectric point

fluid compartment to the bloodstream through the arachnoid granulations at the superior sagittal sinus.[6] Another traditional approach for drug delivery are liposomes.[7] Liposomes, however, are too large to traverse the blood-brain barrier and have not been proved to be effective neuropharmaceutical delivery vehicles.[1]

The importance of developing effective neuropharmaceuticals and the lack of efficacy of existing strategies for drug delivery to brain emphasize the need to develop new approaches to drug transport across the blood-brain barrier. Two approaches discussed in this review have emanated as practical applications of fundamental basic blood-brain barrier research. The first approach is using chimeric peptides as a vehicle for neuropharmaceutical delivery through the blood-brain barrier. The second is biochemical opening of the blood-brain barrier.

Chimeric Peptides

Chimeric peptides are formed when a nontransportable pharmaceutical peptide—for example, β-endorphin for the treatment of pain—is coupled to a blood-brain barrier transport vector.[8] The latter is a peptide or plasma protein that normally enjoys receptor-mediated or absorptive-mediated transcytosis through the blood-brain barrier. Examples of compounds that traverse the blood-brain barrier by receptor-mediated transcytosis include insulin,[9] transferrin,[10] a monoclonal antibody to surface epitopes of the transferrin receptor,[11] and possibly insulin-like growth factors.[12] Proteins that traverse the blood-brain barrier via absorptive-mediated transcytosis include polycationic proteins, such as histone,[13] cationized albumin,[14] cationized antibodies,[15] or lectins, such as wheat germ agglutinin.[16] Although native albumin, which is an acidic protein with an isoelectric point (p^I) of 4 to 5, does not normally cross the blood-brain barrier, chemical modification of the protein, which results in the formation of cationized albumin, $p^I = 8$ to 9, causes the protein to undergo absorptive-mediated transcytosis through the blood-brain barrier.[14,17] More recent studies have shown that an antitransferrin receptor antibody[11] undergoes receptor-mediated transcytosis through the blood-brain barrier at rates that are severalfold faster than the transport of cationized albumin.[18]

Proteins such as cationized albumin or antitransferrin receptor monoclonal antibodies may be used as a vector to ferry across the blood-brain barrier compounds that are pharmacologically active in brain (Figure 1).[19] The four steps of the chimeric peptide transport process are receptor-mediated endocytosis at the blood side of the blood-brain barrier; receptor-mediated exocytosis of the chimeric peptide at the brain side of the blood-brain barrier with release into brain interstitial fluid; thiol-based cleavage of the disulfide bond adjoining the chimeric peptide, which results in the release within brain of pharmacologically active peptide; and binding of the pharmacologically active peptide to its cognate receptor in brain after release from the vector. Previous studies have provided evidence that a β-endorphin cationized albumin chimeric peptide undergoes absorptive-mediated endocytosis and exocytosis at the blood-brain barrier in vivo. Also, the brain contains the necessary disulfide reductases that are sufficiently active to cleave the chimeric peptide, which results in the release of free β-endorphin from its cationized albumin vector.[19] Cationized albumin has proved to be an effective blood-brain barrier transport vector for experimental studies in laboratory animals. The use of this vector in humans may be limited by the rapid renal uptake of cationized albumin, however.[17] While highly cationic proteins are known to be nephrotoxic,[20] recent studies have shown that mildly cationized homologous albumins may be administered repetitively to laboratory animals without measurable nephrotoxicity.[17] Nevertheless, it would be advantageous to develop vectors with a higher degree of brain specificity. Developing such vectors may invariably arise from a molecular biologic analysis of brain capillary-specific proteins. The production of monoclonal antibodies to brain capillary-specific proteins may prove to be brain transport vectors with a high degree of brain specificity.

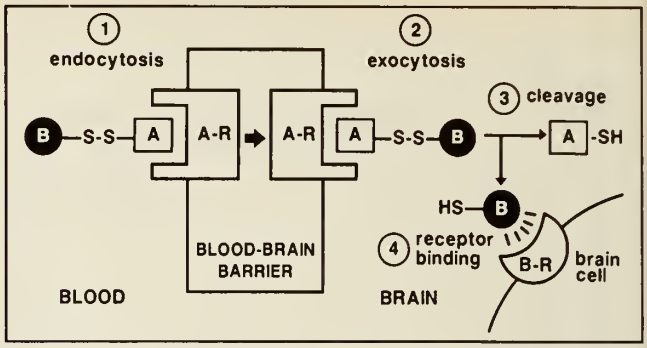

Figure 1.—The delivery of chimeric peptide through the blood-brain barrier is viewed as a process composed of 4 overall steps (see text). **A** is a transportable vector, for example, antitransferrin receptor monoclonal antibody; **B**, nontransportable (pharmacologically active) peptide, for example, β-endorphin; **A-R**, peptide A, for example, transferrin receptor; **B-R**, peptide B receptor (from Pardridge et al[19]; reproduced with permission from *Endocrinology*).

Blood-Brain Barrier Glucose Transporter, a Model Brain Capillary-Enriched Protein

RUBEN J. BOADO, PhD*: A vector with a relatively high degree of brain specificity is a monoclonal antibody to the transferrin receptor.[11] The transferrin receptor is a brain capillary-enriched protein,[21] that is, a protein found in high concentration in brain capillary endothelium relative to neurons or glial cells or to microvascular endothelium in peripheral tissues. Other brain capillary-enriched proteins are listed in Table 2.[1,21-33] When sections of animal or human brain are stained with antibodies to these proteins, the microvascular endothelium is markedly illuminated owing to the high concentration of these proteins in brain capillary endothelium. The brain capillary-enriched proteins, however, may also be localized in peripheral tissues. In contrast, brain capillary-specific proteins are thought to be expressed only in the brain capillary endothelium and not in peripheral tissues, and two brain capillary-specific proteins have been identified (Table 2).

The identification and molecular cloning of brain capillary-specific protein genes may lead to the development of monoclonal antibodies specific to these proteins. The molecular cloning of brain capillary-specific protein genes requires the development of brain capillary complementary DNA

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TABLE 2.—*Brain Capillary-Enriched Proteins and Brain Capillary-Specific Proteins**

Functional Class	*Protein*
Brain Capillary-Enriched Proteins	
Nutrient transporters	GLUT-1 glucose transporter
	Low Km NAA transporter
Peptide transporters	Transferrin receptor
	Insulin receptor
Drug transporters	P-glycoprotein (MDR gene product)
Vitamin transporters	Cellular retinol binding protein
Cholesterol transporters	Apolipoprotein A-I
Enzymes	γ-Glutamyltranspeptidase
	Aminopeptidase M
Phosphoproteins	50-55 KDa triplet
HLA antigens	Class I (endothelium)
	DR-antigen (pericyte, smooth muscle)
Surface antigens	CD36
	HT7
	140 KDa pericyte protein
	25 KDa triplet
Brain Capillary-Specific Proteins	
Surface antigens	45 and 53 KDa proteins

MDR = multidrug resistance, NAA = neutral amino acid

*From Pardridge,[1] compiled from data in references 21-33.

(cDNA) libraries. It is probably not possible to isolate cDNA clones corresponding to brain capillary-specific protein genes by screening cDNA libraries made from total brain. The volume of the brain capillary endothelial cell is only about 1 μl per gram of brain. There is only approximately 1 ml of endothelial cytoplasm in an entire human brain and only 1 μl of endothelial cytoplasm in an entire rat brain.[1] Therefore, less than 0.2% of the cDNA clones in a total brain library may be derived from reverse transcription of brain capillary-derived messenger RNA (mRNA). Consequently, it is necessary to isolate mRNA density from brain capillaries, which may be isolated from either laboratory animal or human autopsy brain (Figure 2).[34] Messenger RNA has been directly isolated from either bovine or pig brain capillaries, and blood-brain barrier cDNA libraries have been prepared in λgt10[32] or λgt11 vectors.[33] From these libraries, several brain capillary-enriched protein gene cDNAs have been cloned, including those for γ-glutamyl transpeptidase,[24] the GLUT-1 glucose transporter,[33,35] and apolipoprotein A-I.[32]

The blood-brain barrier GLUT-1 glucose transporter may be a brain capillary-enriched protein target for drug delivery because recent studies have shown the concentration of this protein in brain microvessels is particularly high, for example, 10 picomol per mg of protein.[36] Thus, the concentration of the GLUT-1 glucose transporter is approximately 100-fold more abundant than is the transferrin receptor.[37] In addition, the GLUT-1 glucose transporter protein is expressed selectively in brain microvascular endothelium with minimal, if any, expression in neurons or glial cells. Recent quantitative Western blotting, in situ hybridization, quantitative Northern blotting, and quantitative electron microscopic immunogold studies have all indicated that the GLUT-1 glucose transporter is selectively expressed in brain microvascular endothelium with no measurable expression in neurons or glial cells.[36,38,39] The GLUT-1 glucose transporter protein, however, is also expressed in peripheral tissues, including perivenous hepatocytes, renal collecting duct epithelium, peripheral nerve perineurium, syncytiotrophoblast of the placenta, placenta-fetal microvascular endothelium, and testicular microvascular endothelium.[40] Therefore, although the GLUT-1 transporter protein is specific to endothelium with respect to neurons or glial cells, it is also found in various epithelial and endothelial cells in peripheral tissues.

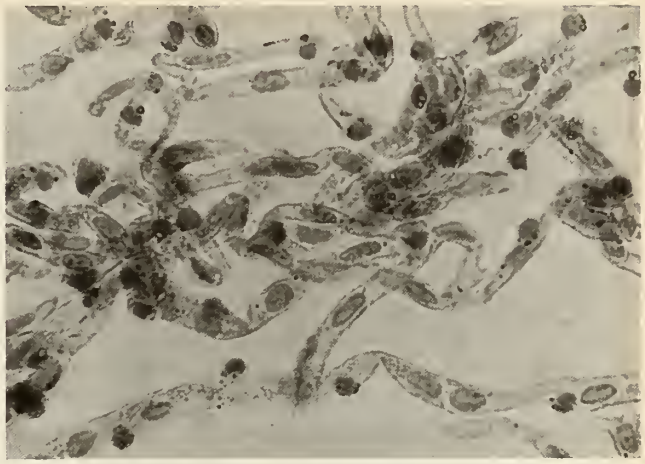

Figure 2.—A light micrograph shows capillaries isolated from a human brain at autopsy. The microvessels are comprised of endothelial cells and pericytes (in an approximate 3:1 ratio) encased in a common basement membrane (magnification × 500; from Pardridge et al[34]; reproduced with permission from *Journal of Neurochemistry*).

Biochemical Opening of the Blood-Brain Barrier—Leukotrienes

KEITH L. BLACK, MD*: Capillaries within primary tumors contain a blood-tumor barrier that impairs delivery of antitumor compounds to neoplastic cells within the brain.[41-43] The inability to delivery antineoplastic drugs across the blood-tumor barrier has led to experimental attempts to open the barrier.[44,45] One approach has used intracarotid infusion of mannitol, which causes a transient osmotic shrinkage of the brain capillary endothelial cells and disrupts the blood-brain barrier tight junctions in normal brain, as well as in brain tumors.[43,45-47] The osmotic barrier disruption approach nonspecifically increases the delivery of chemotherapeutic compounds and monoclonal antibodies to brain.[44] Osmotic disruption of the blood-brain barrier, however, results in only a modest increase in drug levels within the actual tumor, compared with the relatively large increase in drug levels in normal brain.[48] Therefore, this technique increases the exposure of the normal brain parenchyma to the deleterious effects of the chemotherapeutic compounds,[46] whereas suboptimal drug levels may actually reach the tumor. We recently described an experimental method that circumvents this problem and uses leukotrienes to selectively open the barrier within the tumor while leaving the normal blood-brain barrier intact.[49]

The rate-limiting step in leukotriene production is the 5-lipoxygenase enzyme. Brain lipids are rich in membrane-bound arachidonic acid. During a variety of metabolic events, arachidonic acid is released from cell membranes by phospholipase A2 of phospholipase C. Free arachidonic acid, once released, is either reincorporated into the cell membrane or oxidized by one of two pathways: the cyclooxygenase pathway to prostaglandins or the 5-lipoxygenase pathway to leukotrienes. The 5-lipoxygenase pathway—requiring molecular oxygen and calcium—generates the hydroxyleuko-

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triene B4 and the peptidoleukotrienes C4, D4, E4, and F4 via the epoxide intermediate leukotriene A4. The blood-brain barrier γ-glutamyl transpeptidase (Table 2) inactivates leukotriene C4 to leukotriene D4 and leukotriene E4 to leukotriene F4.[50] This enzyme is unique to brain capillaries as it is not present in systemic capillaries.[51]

Leukotrienes are quite potent in their ability to increase vascular permeability in systemic (noncerebral) capillaries.[52] Normal brain capillaries, however, resist the efforts of leukotrienes to increase their vascular permeability. In effect, normal brain capillaries seem to contain an "enzymatic barrier" that inactivates vasoactive compounds such as leukotriene C4. Injured brain capillaries or capillaries in brain tumors lose their "enzymatic barrier" and show increased vascular permeability after leukotriene C4 infusions.[49]

In human brain tumors, a correlation between brain edema and tissue levels of leukotriene C4 has been shown.[53] An index of peritumoral edema was estimated from preoperative contrast-enhanced computed tomographic scans. There was a significant correlation between edema and the log leukotriene C4 levels, with $P < .003$ in all patients. Metastatic tumors had the highest leukotriene C4 level at 13.8 ± 8.5 pg per mg of tissue (mean $\pm$ standard error) and the highest index of edema at 5.7 ± 1.8. The mean leukotriene C4 level in gliomas was 6.2 ± 2.3 pg per mg of tissue and the edema index was 2.1 ± 0.6. There was no edema, no tumor in the temporal lobes removed for seizure, and their level of leukotriene C4 was 0.4 ± 0.1 pg per mg of tissue. These data show that the formation of leukotriene C4 is stimulated by intracranial tumors.

In experimental brain tumors in rats (C6 glioma, RG-2 glioma, and Walker 256 metastatic tumor) γ-glutamyl transpeptidase could not be shown within tumor capillaries.[49] Because brain tumors stimulate leukotriene C4 formation, and tumor capillaries—unlike normal brain capillaries—lack γ-glutamyl transpeptidase to inactivate leukotriene C4, leukotrienes could play an important role in the development of vasogenic edema surrounding brain tumors and in increasing capillary permeability within tumors.

It is important for delivery of antitumor compounds to have the ability to further open the capillary barrier within tumors. Recently intracarotid infusions of leukotriene C4 were shown to selectively open the blood-tumor barrier in rats with RG-2 gliomas.[49] Blood-brain and blood-tumor permeability was determined by quantitative autoradiography using ^{14}C aminoisobutyric acid. Leukotriene C4 (total dose, 4 μg) infused into the carotid artery ipsilateral to the tumor increased twofold the unidirectional transfer constant for permeability within the tumor, whereas no effect on permeability was seen in normal brain. No γ-glutamyl transpeptidase activity was seen in tumor capillaries, in contrast to high γ-glutamyl transpeptidase in normal brain capillaries. These findings support the hypothesis that normal brain capillaries resist the vasogenic effects of leukotriene C4, whereas leukotriene C4 may increase permeability in tumor capillaries.

Loss of γ-glutamyl transpeptidase is not, however, limited in brain to tumor capillaries. γ-Glutamyl transpeptidase activity is also decreased in capillaries in ischemic tissue at 48 and 72 hours after middle cerebral artery occlusion in rats.[54] In comparison, high γ-glutamyl transpeptidase in normal brain capillaries and moderate γ-glutamyl transpeptidase in capillaries in ischemic tissue 24 hours after middle cerebral artery occlusion was reported. At 72 hours after middle cerebral ischemia, the infusion of leukotriene C4 (total dose, 4 μg) into the carotid artery ipsilateral to the ischemia selectively increased blood-brain barrier permeability approximately threefold within core ischemic tissue and tissue adjacent to the ischemic core.[54] No effect on blood-brain barrier permeability was seen within nonischemic brain tissue or in ischemic tissue after only 24 hours of ischemia.

Acivicin is an inhibitor of γ-glutamyl transpeptidase.[54] When rats are pretreated with acivicin, the ability of leukotriene C4 to increase blood-brain barrier permeability in ischemic brain even at 24 hours is significantly enhanced. At 24 hours, when only a moderate reduction in γ-glutamyl transpeptidase has occurred, further blocking of γ-glutamyl transpeptidase activity with acivicin results in a significant enhancement of the ability of leukotriene C4 to open the blood-brain barrier.[54]

These experiments show that brain capillaries contain an "enzymatic barrier" that inactivates vasoactive compounds, like leukotrienes, which increase blood-brain barrier permeability. In some pathologic conditions—that is, brain tumors, ischemia—this "enzymatic barrier" is lost. One component of the enzymatic barrier seems to be γ-glutamyl transpeptidase. Its loss in tumor capillaries and in ischemia permits leukotriene C4 to increase vascular permeability in these conditions and produce vasogenic edema. Because leukotriene C4 production is significantly increased in brain tumors, leukotrienes may play an important role in edema surrounding brain tumors. Clinically important, the selective vulnerability of tumor capillaries to leukotrienes can be used therapeutically. Because tumor capillaries in brain tumors form a barrier to many chemotherapeutic compounds and monoclonal antibodies, leukotriene C4 may be used to open selectively the barrier within tumors while leaving the normal blood-brain barrier intact. One important advantage of selective barrier opening would be protecting normal brain tissue from the potentially deleterious effects of antineoplastic compounds.

Biochemical opening of the blood-brain barrier by vasoactive substances such as leukotrienes may involve cell-to-cell interactions at the cerebral microcirculation. The latter is comprised of at least four cell types: endothelium, which constitutes the permeability barrier; astrocyte foot processes, which invest more than 95% of the surface of the brain capillary; pericytes, which have contractile and phagocytic functions at the microcirculation; and nerve endings, which directly innervate brain microvascular endothelium.[1] To understand the mechanisms of cell-to-cell interactions at the brain microcirculation, in vitro tissue culture models have been established to investigate the cell biology of endothelium-astrocyte interactions.

Cell Biology of Brain Endothelium and Astrocyte Interactions

Pasquale A. Cancilla, MD*: Our laboratory has used in vivo and in vitro systems to explore the complex interactions that occur between endothelial cells and astrocytes and that lead to the development of properties associated with the blood-brain barrier. The in vivo system most often used by us has been the localized application of liquid nitrogen to the intact skull of the mouse to produce a discrete freeze injury.[55]

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This area of injury undergoes a reproducible series of changes including necrosis, monocyte-macrophage infiltration, endothelial proliferation and neovascularization, and astrocyte proliferation and migration that lead to restitution of endothelial-astrocyte relations and restoration of the blood-brain barrier. Our studies used ^{3}H-thymidine as a marker for the initiation of DNA synthesis in endothelial cells and astrocytes at intervals after the injury.[56,57] Both endothelial cells and astrocytes are normally quiescent cells that quickly return to the mitotic pool in response to injury. This coincides with the migration of monocyte-macrophage into the area of injury from the circulation. Interruption of the monocyte-macrophage response reduces the endothelial response to approximately 10%. Thus, factors derived from the monocyte-macrophage are operational in the endothelial response. Cytokines may also be involved in restoring the endothelium of the injured vessels and in neovascularization because in-vitro studies have shown a chemotactic effect of monocyte-macrophage on endothelium.[58]

The astrocytes adjacent to the area of injury undergo a similar ^{3}H-thymidine incorporation after an injury, but the maximum response is of lower magnitude (10%) and occurs later—day 5 compared with day 3 to 4 after injury—than the endothelial cell response. In vitro studies have shown that cytokines derived from monocyte-macrophage may be operational in this response and that endothelial cells may liberate chemotactic factors, which attract astrocytes from the uninjured brain adjacent to the injured area and to the new vessels.[58] Studies using the freeze-injury model have shown that endothelial cells in vessels adjacent to the injury initially have the enzyme γ-glutamyl transpeptidase, but within five to seven days of the injury, the enzyme is no longer found in the endothelium.[57] This corresponds to the time when the endothelial cells migrate into the area of injury as part of the process of neovascularization and correlates with the loss of contact of the astrocyte with the endothelium.[56] When the astrocyte reestablishes contact with the endothelial cell, γ-glutamyl transpeptidase is found once again in the endothelium.[57] This supports the in vivo findings that interaction of the astrocyte with the endothelial cell is necessary for the induction and maintenance of γ-glutamyl transpeptidase expression and that a factor liberated by the astrocyte is responsible for this effect.[59,60]

Endothelial cells influence responses in the astrocyte. Media conditioned by cerebral endothelial cells contain a factor or factors that stimulate the incorporation of ^{3}H-thymidine by the astrocyte.[61] This factor is a peptide of greater than 50,000 molecular weight that is destroyed by protease digestion and is different from other known growth factors. Rather than stimulating ^{3}H-thymidine incorporation in endothelial cells through an autocrine effect, the factor does not affect endothelial cells.

Dr Takashi Minakawa, in our laboratory, has used his model of developing vascular-like structures in vitro into a model replicating the relation of the vascular endothelium and astrocytes.[62] The system used gelatin-coated slides in chambers as a base for developing branching tube-like structures when coated with vitrogen. Astrocytes or pericytes added to the surface of the vitrogen migrate through this layer and develop contacts with the endothelial structures. Astrocytes and pericytes respond differently. By 24 hours after the random addition of the pericytes to the system, 100% of the cells are in contact with the endothelium. Astrocytes are slower to respond because 10% are in contact by 5 hours, 75% are associated with the vessels at 24 hours, and 93% by 6 days.

A chemotactic assay has been developed using several features from this system.[62] Use of it has shown that these vascular-like structures, but not monolayer cultures of endothelium, release a chemotactic factor involved in the attraction of the astrocyte to the endothelium. This factor is liberated from the better-differentiated cells forming the vascular tubes and suggests that the response is coordinated and may serve to attract the astrocyte to the endothelium, as was suggested by the in vivo model.

The studies described in this presentation represent some, but not all, of the types of studies that have been done to show that the cell-to-cell interaction between endothelium and astrocyte is important in establishing and maintaining the blood-brain barrier.[63-68] Many investigators are interested in this area, so we may soon see important and detailed reports describing not only the cell biology but also the molecular mechanisms of these complex and fascinating relations.

Ongoing basic research into the molecular and cell biology of the blood-brain barrier is expanding further the definition of brain capillary-specific proteins and the molecular mechanisms involved in paracrine cellular interactions at the level of the cerebral microcirculation. This research invariably provides insights into the pathogenesis of brain diseases.[63] Basic research in blood-brain barrier molecular and cell biology has also led to new approaches to brain drug delivery. As molecular and neurobiologic research further defines the mechanisms of disorders of the brain, new therapies may emerge. An essential component for developing neuropharmaceuticals of the future will be integrating these with the emerging paradigms of blood-brain barrier drug delivery.

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Clinical Significance in Alcoholic Patients of Commonly Encountered Laboratory Test Results

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An improved understanding of medical problems of alcoholic patients can be gained from commonly encountered laboratory test results. Liver function tests—such as measures of alkaline phosphatase, γ-glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase—may provide evidence of altered hepatic activity of different types, such as obstruction and hepatocellular injury. Other test results may indicate impaired hepatic function, such as measurements of albumin, bilirubin, prothrombin time, and blood urea nitrogen. Alterations are also common in electrolytes, blood glucose, magnesium, phosphate, uric acid, and acid-base balance. Disturbances in hematologic function are not infrequent in alcoholic patients, including anemias from many causes, altered granulocyte responses, and thrombocytopenia.

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Alcoholism continues to be a major health problem in the United States, and excessive use of alcohol can adversely affect multiple organ systems. Numerous laboratory results may be abnormal in alcoholic patients. In this article we review the tests that are commonly performed in alcoholic patients seeking health care, especially in an inpatient setting. The discussion will emphasize the clinically useful information that can be gained from each test to allow for a better understanding of medical problems and management decisions in alcoholic patients.

Testing for Hepatic Damage or Function

The following tests, traditionally called liver function tests, are indicators of altered hepatic activity rather than hepatic function: alkaline phosphatase, γ-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST, formerly SGOT), and alanine aminotransferase (ALT, formerly SGPT). Other tests may provide an indication of hepatic function (Table 1).

Alkaline Phosphatase

Hepatic steatosis, without evidence of inflammation or cirrhosis, is not usually associated with an elevation of the alkaline phosphatase level.[1] With hepatocellular damage from alcohol, the alkaline phosphatase level usually increases but to a lesser degree than in cholestatic and infiltrative disorders of the liver, in which it is generally elevated to three or more times above the upper limits of normal.[2] In patients with alcoholic hepatitis, alkaline phosphatase levels tend to be less than two times normal[3] and do not correlate well with the level of bilirubin.[4] In a small group of these patients, however, the alkaline phosphatase level may be elevated in a cholestatic fashion without other recognized causes of cholestasis.[4-7] This is likely related to long-term ethanol ingestion inducing substantial hepatic architectural distortion due to inflammatory infiltration and fibrotic changes.

TABLE 1.—*Laboratory Indicators of Hepatic Function*

Serum albumin	Bilirubin
Prothrombin time	Blood urea nitrogen

γ-Glutamyl Transpeptidase

γ-Glutamyl transpeptidase levels are more hepatic specific than alkaline phosphatase levels. This may be the only hepatic enzyme elevated with alcohol use, although it does not discriminate alcoholic liver disease from other forms of liver disease. Elevation of GGT levels initially results from enzyme induction by alcohol and not from hepatic damage or cholestasis.[8] An elevated GGT level that returns to normal[9] is a reliable indicator of abstinence or a substantial reduction in drinking. A GGT level that remains elevated in the presence of abstinence may warrant further diagnostic consideration of alcoholic liver disease or liver disease from other causes.[10] Because of the questionable reliability of assessing alcohol intake based on patient interviews, elevated GGT levels in patients with previous alcohol-related problems who claim abstinence may indicate continued drinking, ongoing alcoholic liver disease in the presence of abstinence, or the presence of unrelated liver disease.[1,11-15]

Aspartate Aminotransferase

With alcoholic hepatitis, the AST level is commonly from two to ten times normal but rarely higher, even in the presence of severe alcoholic hepatitis.[4,14,16,17] It is commonly thought that an elevated AST level signifies the presence of alcoholic hepatitis, which carries an increased risk for developing cirrhosis.[18] The AST level can be elevated, however, when only alcoholic fatty infiltration or foamy degenerative changes are identified on liver biopsy, without the inflammatory component of alcoholic hepatitis or elevation of the alkaline phosphatase level.[1,19] Some patients with predominantly

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
AST = aspartate aminotransferase
BUN = blood urea nitrogen
GGT = γ-glutamyl transpeptidase
MCV = mean corpuscular volume

alcoholic cirrhosis may not have AST level elevations. This may be attributable to an inadequate hepatocyte mass to produce sufficient spillage of enzyme after long-standing alcohol-induced hepatic damage. When the absolute value of AST is elevated to a level of tenfold or greater above normal, other causes of hepatocellular injury—such as viral, drug, or toxin—should be considered, separate from or in addition to alcohol.[9]

Alanine Aminotransferase

The ALT level is a more specific indicator of hepatic disease than is the AST. In an alcoholic patient, however, the ALT level is usually elevated to a lesser degree than the AST level and may be within normal limits.[4] Typically the AST-to-ALT ratio is approximately 1.5 or 2 to 1 in alcoholic liver disease,[17,20,21] even when neither level is elevated.[21] When the AST-to-ALT ratio is less than or equals 1 to 1, other causes of hepatocellular injury should be considered.

Lactate Dehydrogenase

The level of lactate dehydrogenase is not sufficiently specific as an indicator of hepatic injury and often is overinterpreted. It provides no useful information in addition to the aminotransferase levels in evaluating for known or suspected alcoholism. When the lactate dehydrogenase level is disproportionately elevated relative to the aminotransferase levels, other nonalcohol-related hepatic infiltrative processes, such as metastatic carcinoma, or nonhepatic causes should be considered.

Albumin

The serum albumin level in patients with alcoholic hepatitis or cirrhosis is often moderately to severely reduced, frequently in the range of 20 to 30 grams per liter (2 to 3 grams per dl).[4] This results in low oncotic pressure, which—together with increased portal pressures, increased sodium retention, and impaired peritoneal lymphatic drainage—is one of the primary accountable factors for the development of ascites.[22] The reduced levels of albumin can be caused by impaired hepatic synthesis, shunting into the peritoneal space, protein malnutrition, malabsorption, or albuminuria.[23] In the absence of malnutrition, a protein-losing enteropathy, or renal loss of albumin, a low albumin level that does not improve rapidly with good nutrition indicates a poor prognosis because it denotes severely impaired hepatic synthetic function. While the serum aminotransferase and alkaline phosphatase levels may be strikingly abnormal despite preservation of hepatic synthetic function, they conversely may remain normal despite seriously impaired hepatic function in persons with alcoholic liver disease.

Prothrombin Time

In addition to a lowered serum albumin level, a prolonged prothrombin time is usually indicative of severely impaired hepatic function in alcoholic patients.[4,24] Failure of a prolonged prothrombin time to become normal after vitamin K is administered to patients with alcoholic liver disease confirms the presence of severely impaired hepatic function.[25] Correction with vitamin K suggests that the prolonged prothrombin time is caused by malnutrition or malabsorption.

Bilirubin

In healthy adults, virtually all of the measured serum bilirubin is unconjugated.[26] In contrast, in patients with alcoholic liver disease, serum bilirubin levels are frequently elevated, with widely variable degrees of conjugation. Occasionally, patients with alcoholic hepatitis develop disproportionate elevations of conjugated bilirubin, producing a cholestatic pattern.[27] When this occurs, the possibility of a concomitant obstructive process of the hepatobiliary tract should be considered.

In a Veterans Affairs cooperative study, clinical jaundice was present in only 13.5% to 19% of patients with alcoholic hepatitis.[25,27] Patients with alcoholic hepatitis who presented with intrahepatic cholestasis, however, were much more likely to be jaundiced and to show evidence of malnutrition, and they had more prolonged prothrombin times, lower levels of albumin, and greater elevations of serum aminotransferase and alkaline phosphatase levels.[27] Of patients who died, 95% were jaundiced, with a mean total bilirubin level of 450 μmol per liter (26.4 mg per dl).[25] In patients with alcoholic hepatitis, a bilirubin level of greater than 86 μmol per liter (5 mg per dl) appears to identify patients with a poor prognosis.[25,27]

Blood Urea Nitrogen

Although the BUN level commonly is not thought of as being affected by hepatic disease, very low BUN levels may provide another indication of severely impaired hepatic function in patients with alcoholic liver disease. A low BUN level is a result of the liver's inability to manufacture urea normally from products of protein and amino acid catabolism. A low BUN level in a patient with alcoholic liver disease, therefore, may indicate impaired hepatic function. In such patients, a high "normal" BUN level may actually represent impaired renal function or prerenal azotemia, usually from excessive diuresis. In alcoholic patients with low baseline BUN levels, volume depletion may not result in the usual disproportionate rise of the BUN in relation to serum creatinine levels seen with prerenal azotemia. In patients with alcoholic hepatitis, BUN levels around 10.0 to 11.0 mmol per liter (mid-30s mg per dl) and creatinine levels near 260 μmol per liter (3 mg per dl) are associated with a much higher mortality rate than in patients with laboratory values without such elevations.[25] Therefore, knowing a patient's previous BUN level is important to interpret current levels correctly.

In patients with alcoholic liver disease, nonsteroidal anti-inflammatory drugs may cause a deterioration in renal function with an elevation of the BUN level due to the inhibitory effects of these drugs on intrarenal vasodilatory prostaglandins. Because prostaglandins are of critical importance for preserving renal function in patients with cirrhosis and ascites,[28,29] nonsteroidal anti-inflammatory drug use should be avoided in patients with known alcoholic liver disease, especially in the presence of ascites. If these drugs are used, renal function must be monitored very closely. Reversible, transient reductions in renal function induced by nonsteroidal

anti-inflammatory drug use may identify a subgroup of patients with a poor prognosis.[29]

Measuring Electrolytes, Glucose, and Minerals

Sodium

Hyponatremia is common in cirrhotic patients. Some of these patients who have ascites have an impaired ability to excrete free water, at least partially caused by nonosmotic baroreceptor stimulation of vasopressin due to a decrease in effective plasma volume.[30] This vasopressin response correlates with greater amounts of ascites, low serum albumin levels, higher pulse rates, and higher plasma renin and aldosterone levels.[30] Other causes of hyponatremia in patients with alcoholic liver disease are the use of diuretic or antidiuretic drugs and large-volume paracentesis.

In alcoholic patients with ascites, a serum sodium level of less than 130 mmol per liter (130 mEq per liter) generally reflects the inability of the kidneys to handle free water, making water restriction a necessary consideration. Because hyponatremia in patients with alcoholic cirrhosis may increase the risk of mortality,[31] especially in association with a low glomerular filtration rate,[32] serum sodium levels should be monitored carefully in hyponatremic alcoholic patients. This is especially important for those receiving concomitant diuretic therapy or paracentesis of large volumes of ascitic fluid.

Urine sodium excretion may also provide prognostic information in a nonazotemic cirrhotic patient with ascites who is not yet receiving diuretic agents. In those patients with a urine sodium excretion of less than 10 mmol per day (10 mEq per day), indicating high renin to angiotensin activation, Arroyo and co-workers[32] found a 50% survival rate of approximately 6 months compared to 28 months in those with a higher urine sodium, or less renin-angiotensin activation. No other clinical clue has been shown to discriminate between such patients, who otherwise appear similar clinically. The lower the urine sodium level, the greater the activation of the angiotensin-aldosterone system,[33] and in this setting of renin-angiotensin system activation, it is more appropriate to use spironolactone, an aldosterone antagonist, for treating ascites initially, rather than other diuretic agents.

Potassium

Whole-body potassium stores are often depleted in alcoholic patients with cirrhosis and ascites.[34] Initial serum potassium levels in patients admitted to hospital may be low due to secondary hyperaldosteronism associated with ascites, volume depletion from vomiting or diarrhea, use of non–potassium-sparing diuretic agents, or inadequate diet.[34] In a cirrhotic patient with ascites, using the aldosterone antagonist diuretic spironolactone or restricting sodium intake will help conserve potassium. Therefore, it is important for such patients not only to restrict sodium intake but also not to replace table salt with salt substitutes because all such preparations contain potassium. Clinically significant hyperkalemia may result if these restrictions are not applied. Angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs also should be avoided with the use of spironolactone and salt restriction because they increase the risk of developing hyperkalemia by their hypoaldosterone effect[35] and their effects on intrarenal prostaglandins,[29] respectively.

Glucose

Alcohol-induced hypoglycemia occurs in only 1% of long-term alcoholic patients but can be severe, with a mortality rate of 10%.[36,37] This condition can occur in nonalcoholic persons ingesting alcohol, as well, especially in those with poor caloric intake. Alcohol impairs gluconeogenesis by altering the NADH-NAD (reduced form of nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide) ratio, inhibiting the release of alanine from muscles, which is required as a precursor for gluconeogenesis. This altered ratio also inhibits hepatic uptake of the precursors lactate, glycerol, and alanine. Hypoglycemia occurs only when hepatic glycogen stores are depleted and caloric intake has been minimal for at least 12 hours before drinking.[38] Signs of hypoglycemia, such as mental dysfunction, tremor, headache, tachycardia, and diaphoresis, may appear as long as 30 hours after alcohol ingestion.[39] Ketosis is often present as well (this is discussed in more detail later). The blood ethanol level is usually undetectable or low but may be mildly elevated at the time of onset of symptoms. Care must be taken in discriminating between hypoglycemia and alcoholic withdrawal because their clinical manifestations can be similar. Other causes of hypoglycemia in alcoholic patients include starvation, impaired hepatic synthetic function from alcoholic liver disease, hepatoma, sepsis, or drug-induced liver disease.[40]

In contrast, excessive alcohol intake may result in hyperglycemia, which occurs only in persons with an underlying glucose intolerance or unrecognized diabetes.[41] Alcohol may impair the conversion of glucose to glycogen, allowing elevations of blood glucose after carbohydrate loading in susceptible persons.[38]

Uric Acid

Hyperuricemia may be observed after acute alcohol ingestion in nonalcoholic persons or with long-term ethanol use, although its frequency is not established.[42-45] The mechanism of alcohol-induced hyperuricemia appears to be an increase in urate synthesis caused by an increase in the turnover of adenine nucleotides.[42] Other possible contributing factors include decreased renal uric acid excretion resulting from increased lactate production[46] and increased substrate for uric acid production, such as the high purine content in beer. In persons who regularly ingest illicit whiskey ("moonshine"), hyperuricemia may develop secondary to impaired urate clearance from lead nephropathy caused by the high levels of lead found in moonshine.[47] Gout may develop and, in this context, is known as saturnine gout.[48] Increases in uric acid levels often parallel increased alcohol consumption, although the mean level may remain within the normal range.[44] The risk for developing gout in alcoholic patients with hyperuricemia drinking commercial alcoholic beverages is not greater than that of nonalcoholic persons with similar levels of hyperuricemia.[44] Individual attacks of gout, however, can undoubtedly be triggered by alcohol.

Phosphate

Severe hypophosphatemia is relatively uncommon in nonalcoholic hospital patients.[49,50] In contrast, hypophosphatemia is not uncommon in the alcoholic patient[50,51] and in one study was present in 30% of alcoholic men admitted to a general medicine ward.[49] These patients are typically in alco-

hol withdrawal with intracellular shifts of phosphate associated with respiratory alkalosis. Hypophosphatemia is often not present on admission but may develop within several days after refeeding when there is inadequate phosphate supplementation.[49] Therefore, initially normal serum phosphate values should be rechecked within several days, since there may be no clinical clue to the development of hypophosphatemia.

In hypophosphatemia total-body phosphate stores are underestimated as determined by muscle content.[52] With long-term alcohol use, phosphate depletion may result from insufficient dietary intake, impaired intestinal absorption because of vomiting, diarrhea, use of phosphate-binding antacids, increased cellular uptake due to respiratory alkalosis, and increased urinary phosphate losses caused by alcohol directly.[53,54] Metabolic acidosis may further enhance this alcohol-caused renal loss of phosphate by reducing intracellular phosphorylation, creating an intracellular-to-extracellular shift of phosphate.[55] Phosphate levels lower than 0.30 to 0.50 mmol per liter (1.0 to 1.5 mg per dl) in alcoholic patients warrant immediate phosphorus repletion to avoid disruptions of cellular function that may result in rhabdomyolysis,[56] myocardial failure,[57,58] arrhythmias,[59] respiratory failure,[60,61] central nervous system dysfunction,[62] metabolic acidosis,[63] hemolysis,[64] impaired erythrocyte oxygen-carrying capacity,[65] and phagocytic dysfunction.[66]

Hyperphosphatemia may also be seen in alcoholic patients on admission to the hospital. Ryback and associates[49] found hyperphosphatemia in 10% of men in an alcoholism treatment program. Factors most likely contributing to this include rhabdomyolysis, metabolic acidosis, and hypomagnesemia. In the subset of alcoholic patients with rhabdomyolysis, hyperphosphatemia results from tissue ischemia and breakdown. In alcoholic ketoacidosis and, to a greater degree, in lactic acidosis, hyperphosphatemia is likely caused by intracellular-to-extracellular shifts of phosphorus.[67]

Magnesium

Hypomagnesemia commonly is seen in hospitalized alcoholic patients, although its true frequency is not known.[52,68] Hypomagnesemia should be suspected and is particularly common in the presence of other electrolyte imbalances, including hypokalemia, hypophosphatemia, hyponatremia, and hypocalcemia.[69-72] Even when a long-term alcoholic patient has normal serum magnesium levels, total body magnesium content may be reduced, particularly that of skeletal muscle. Causes of magnesium deficiency in alcoholic persons include use of diuretic agents, dietary inadequacy, malabsorption, chronic diarrhea, protracted vomiting or nasogastric suctioning, increased cellular uptake from respiratory alkalosis secondary to the hyperventilation associated with alcohol withdrawal states, and increased ethanol-induced renal excretion.[73] Increased urinary excretion of magnesium and calcium is seen after acute alcohol ingestion, regardless of the amount of alcohol consumed.[69]

Alcohol-induced hypomagnesemia produces both a reduction in target organ sensitivity to parathormone and a reduction in parathormone secretion, which results in hyperphosphatemia and hypocalcemia.[74,75] When serum magnesium levels decrease to 0.50 mmol per liter (1 mEq per liter) or less, clinical manifestations of hypomagnesemia occur. These include lethargy, weakness, fatigue, neuromuscular irritability (tetany), reduced mentation, and cardiac arrhythmias.[71] Hypomagnesemia also potentiates the clinical manifestations of hypocalcemia and hypokalemia.[76] Because of the overlapping clinical manifestations of hypomagnesemia, hypophosphatemia, hypocalcemia, and hypokalemia, it may be impossible with combined electrolyte disturbances to discern which is accountable for a particular clinical symptom or sign.[71]

Acid-Base Disturbances

Arterial Blood Gases

Arterial blood gas determinations may reveal several alterations of acid-base balance that are caused by ethanol abuse, although these changes are not direct metabolic effects of alcohol. The frequency of these abnormalities in alcoholic patients is unknown.

Respiratory Acidosis and Alkalosis

Alcohol intoxication may depress respiratory drive by a centrally acting mechanism, resulting in hypoventilation and respiratory acidosis. Hyperventilation is also common, resulting in respiratory alkalosis. This may develop from severe abdominal pain caused by alcoholic gastritis, hepatitis, or pancreatitis, as well as from the alcohol withdrawal state and the associated hyperactivity of the sympathetic nervous system.[77] In some alcoholic patients with cirrhosis, a ventilation-perfusion imbalance develops from intrapulmonary arterial-venous communications.[78] This allows for the development of a hypoxic respiratory alkalotic state.[78]

Moderate hypoxia may occur in patients with cirrhosis.[79-82] In one series of cirrhotic patients, 7% had Po_2 levels lower than 60 mm of mercury.[79] This has been attributed to intrapulmonic vascular and diffusion abnormalities.[78,79] No correlation to the presence or degree of hypoxemia to other hepatic tests has been shown.[82] When the patient is standing, the Po_2 may drop even further (orthodeoxia) from increased flow to the basilar portions of the lung.[82] In a dyspneic, hypoxic patient with alcoholic cirrhosis, other causes may not be present to account for the dyspnea or hypoxia.[79-82]

Metabolic Alkalosis

Metabolic alkalosis may result from volume depletion and hydrochloric acid loss due to ethanol-induced vomiting. This is associated with hypochloremia from upper gastrointestinal loss and hypokalemia from secondary renal losses. The latter is caused by renal activation of renin and angiotensin because of volume depletion with secondary enhanced secretion of aldosterone, which promotes sodium reabsorption in the distal tubules. Potassium is preferentially exchanged for sodium rather than the hydrogen ion because of alkalosis.

Metabolic Acidosis

Metabolic acidosis with or without an anion gap can also be seen as a consequence of alcohol abuse. Non-anion gap metabolic acidosis results from diarrhea or a renal acidification defect,[83] an increased bicarbonate loss associated with phosphate depletion,[84] or excessive use of lactulose to prevent hepatic encephalopathy. When alcohol-related metabolic acidosis is associated with a widened anion gap, a diagnosis of lactic acidosis or ketoacidosis should be consid-

ered. When lactate or ketone levels are not elevated, a history of ingesting ethylene glycol (antifreeze), methanol, or salicylates should be investigated.[85-91] Lactic acidosis may be caused by alcohol-induced impaired hepatic lactate clearance,[88] which is often associated with hypoglycemia.[87,89] As in other patients, lactic acidosis in alcoholic patients may be caused by seizures or by tissue ischemia from hypoperfusion due to hypovolemia or sepsis.[89]

Alcoholic ketosis typically occurs in long-term alcoholic patients who have stopped drinking for several days following a binge of heavy alcohol intake.[85,86,90,91] Because of abdominal pain and vomiting, caloric intake does not resume, resulting in starvation-induced breakdown of peripheral fat stores.[85,90,91] Ketosis is usually not severe, and acidosis may not be present.[85] In fact, ketosis may occur in conjunction with a metabolic alkalosis or respiratory alkalosis from the causes listed previously.[85] Unlike in patients with lactic acidosis, ethanol levels in patients with alcoholic ketosis are usually undetectable or low.[85] Glucose levels may be low, normal, or elevated.[85,87,91] The nitroprusside reaction used to detect ketones may show little or no reactivity despite the presence of ketones because β-hydroxybutyrate is elevated disproportionately to acetoacetate, the other major ketone, and this reaction is insensitive to β-hydroxybutyrate.[90]

The following events contribute to the pathogenesis of alcoholic ketoacidosis[85]: Ethanol impedes hepatic gluconeogenesis, resulting in low serum glucose levels, while insufficient caloric intake depletes hepatic glycogen stores. Ethanol itself, and low insulin levels owing to starvation, lead to increased hepatic production of free fatty acids and peripheral lipolysis of triglycerides to free fatty acids as a fuel source to replace the depleted glucose stores.

The precise role of alcohol in the development of alcoholic ketoacidosis is not known. It is thought that alcohol suppresses ketogenesis and, when alcohol ingestion ceases, ketogenesis ensues with the development of ketoacidosis, as the notably elevated levels of free fatty acids are hepatically converted to ketones.

Complete Blood Count

Hemoglobin, Hematocrit, and Mean Corpuscular Volume

Anemia is common in alcoholic patients and may result from a variety of causes (Table 2). Most common are iron deficiency from gastrointestinal blood loss, anemia of chronic disease, folate deficiency, or a sideroblastic state. In more than half of alcoholic patients who are anemic, more than one cause is present.[92] A peripheral blood smear may reveal mixed populations of erythrocytes.

Mild degrees of macrocytosis, often unassociated with anemia, have been reported in more than 80% of long-term alcoholic patients.[93] Although macrocytosis in such patients may be due to folate or vitamin B_{12} deficiency, the most common cause is alterations in the developing erythrocyte caused by alcohol, independent of liver disease or other known causes of macrocytosis.[93] Macrocytosis of alcoholism occurs in about half of alcoholic patients after several months of drinking. The severity of macrocytosis is usually less than that seen in patients with folate or vitamin B_{12} deficiency, with a mean corpuscular volume (MCV) between 100 and 110 fl. Macro-ovalocytes are seen less frequently in alcoholic macrocytosis than with megaloblastic anemias. The MCV usually returns to normal within three to four months of abstinence, as normal erythrocytes replace macrocytes.[94,95] An elevated MCV correlates closely with duration and extent of drinking episodes; however, it is a relatively insensitive indicator of alcoholism.[96,97] Nevertheless, an elevated MCV without another apparent cause may indicate continued alcohol consumption despite denials by the patient.

TABLE 2.—*Hemotologic Chonges Associoted With Alcoholism*

Erythrocytes Vacuolization of erythroblasts Macrocytosis with or without megaloblastic anemia Microcytosis associated with iron deficiency Normocytic anemia of chronic disease Sideroblastic anemia Hemolytic anemia Mixed anemias	Leukocytes Granulocytopenia Lymphopenia Platelets Thrombocytopenia

Megaloblastic anemia in alcoholic patients is usually caused by folate deficiency, rarely by vitamin B_{12} deficiency.[95] In nonalcoholic patients, megaloblastic anemia typically is diagnosed by identifying macro-ovalocytes and hypersegmented neutrophils on peripheral blood smear and an elevated MCV of 100 to 140 fl. Bone marrow examinations reveal megaloblastic changes. In alcoholic patients, however, these findings are absent with surprising frequency. For example, the MCV is normal in approximately a third of patients with alcohol-related megaloblastic anemia, and only 25% will have an MCV greater than 110 fl.[92] Macro-ovalocytes, typical of megaloblastic anemia, are identifiable in a third of anemic alcoholic patients without megaloblastic changes but are usually fewer in number and percentage. Therefore, while increased numbers of macro-ovalocytes are a sensitive indicator for megaloblastic changes in bone marrow, they are of low specificity.[92]

Hypersegmentation of neutrophils is found in about 80% of alcoholic patients with megaloblastic changes of the bone marrow compared with 5% of alcoholic patients without such bone marrow changes. This effect may last for up to two weeks after patients begin folate treatment and thus may be helpful in reaching a diagnosis, even after folate therapy has been instituted.[92] Otherwise unexplained elevations of serum lactate dehydrogenase levels (isoenzyme LDH-1) may also indicate ineffective erythropoiesis associated with megaloblastic anemia.[95]

Measuring of plasma folate levels in alcoholic patients is not worthwhile because most patients with proven megaloblastic changes will have normal plasma folate levels. In addition, about half of patients with low erythrocyte folate levels have no megaloblastic bone marrow changes.[92] Among those with megaloblastic changes on bone marrow examination and folate levels that are not clearly reduced, few will have confirmed vitamin B_{12} deficiency.

Iron deficiency anemia is not uncommon in alcoholic patients and is usually caused by bleeding from the upper gastrointestinal tract. Dual populations of macrocytic and microcytic cells may be found on examination of the peripheral blood smear resulting in a normal MCV, thereby disguising the presence of microcytes.[98] The classic findings of a low serum iron level and elevated total iron-binding capacity are uncommon in iron-deficient alcoholic patients. The total iron-binding capacity is usually not notably increased, and

serum ferritin levels may be within normal limits as a direct effect of alcoholic liver disease.

Guidelines recently have been recommended for diagnosing iron deficiency in alcoholic patients.[92] Despite the alterations in serum ferritin levels, a value greater than 100 ng per ml virtually excludes an iron-deficient state, whereas a level below 20 ng per ml is so strongly supportive of the diagnosis that further testing to confirm an iron-deficient state is unwarranted. For those with levels between 20 and 100 μg per liter (20 and 100 ng per ml), an elevated total iron-binding capacity is sufficient to confirm the diagnosis. When this level is low or normal, a bone marrow examination is needed to determine the presence of iron stores.[92] An empiric trial of iron replacement with a subsequent increase in reticulocyte count or hemoglobin level also is diagnostic and may obviate the need for a bone marrow examination, but it should not be used without an evaluation for blood loss if iron deficiency is confirmed.

Sideroblastic bone marrow changes are present in about a quarter of long-term alcohol users who are anemic. Sideroblastic anemia, however, is rarely the only cause of anemia in alcoholic patients.[92] Peripheral blood smears typically show dimorphic populations of erythrocytes. Macroovalocytes, transferrin saturation greater than 60%, and serum ferritin levels of more than 300 μg per liter are common. The characteristic increase in serum iron in nonalcoholic sideroblastic anemia is uncommon in long-term alcoholic patients. The cause of sideroblastic changes in persons who abuse alcohol is uncertain and may be a consequence of the toxic effects of alcohol itself.[99] In those drinking "moonshine," lead toxicity may be a contributing factor. In general, sideroblastic changes do not warrant further diagnostic pursuit unless they persist for more than two weeks with abstinence.[92]

Leukocytes

Granulocyte function is often suppressed in alcoholic patients. Granulocytopenia has also been observed in 4% to 8% of alcoholic patients due to the suppressive effect of alcohol on myeloid precursor cells of the bone marrow.[100] Approximately a week is required for granulocyte counts to become normal after alcohol is withdrawn. Alcohol-induced granulocytopenia may be associated with thrombocytopenia and anemia as well, and has been especially associated with severe bacterial infections.[101,102] On the other hand, leukocytosis is found in a third of patients with alcoholic hepatitis and correlates with the severity of disease.[25]

Lymphocyte counts of less than 1.5×10^9 per liter are seen in many alcoholic patients, but lymphocyte counts increase significantly a week after alcohol consumption stops.[98] Lymphopenia, when associated with low body weight, diminished skinfold thickness, hypoalbuminemia, or anergy to common antigens, supports the diagnosis of malnutrition.

Platelets

Thrombocytopenia is a well-recognized sequela of alcohol ingestion.[103] Platelet counts of less than 100×10^9 per liter occur in a quarter of acutely intoxicated patients and 3% of long-term alcoholic patients.[98] These reductions in platelet counts are independent of nutritional state or the presence of liver function abnormalities, anemia, or leukopenia. The basis for thrombocytopenia in such patients may be multifactorial, including a suppressive effect of alcohol on megakaryocyte maturation and platelet release, splenic hypersequestration, folate deficiency, and reduced platelet survival time. The platelet count begins to rise after 2 to 3 days of abstinence and usually reaches its peak in 1 to 14 days. Rebound thrombocytosis—platelet counts up to 900×10^9 per liter—develops in about a third of alcoholic patients who become abstinent, with platelet counts returning to normal in 2 to 3 weeks.[103]

Conclusion

In alcoholic patients, commonly available laboratory tests can provide useful information relating to hepatic damage and hepatic synthetic function. The AST:ALT ratio can help confirm that hepatic injury in an alcoholic patient is, in fact, related to alcohol consumption rather than another cause. Serum electrolyte levels are useful in making decisions regarding a patient's ability to handle free water, potassium needs, and appropriate use of diuretic agents when used for managing ascites. Hypoglycemia, hypophosphatemia, hypomagnesemia, and alterations in a patient's arterial blood gases must be identified because of their potential for impairing important physiologic functions that must be addressed in clinical management decisions.

All hematologic cell lines may be affected by alcohol's effect on the bone marrow, hypersplenism, or nutrition. Anemias are common and often have multifactorial causes. Examination of the peripheral blood smear usually provides excellent clues to the cause, even when more than one factor is contributory.

Readily available laboratory tests are extremely useful for better understanding of physiologic alterations in alcoholic patients and, thereby, allow thoughtful management decisions.

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FINAL NOTATIONS

it will not be simple, it will not be long
it will take little time, it will take all your thought
it will take all your heart, it will take all your breath
it will be short, it will not be simple

it will touch through your ribs, it will take all your heart
it will not be long, it will occupy your thought
as a city is occupied, as a bed is occupied
it will take all your flesh, it will not be simple

You are coming into us who cannot withstand you
you are coming into us who never wanted to withstand you
you are taking parts of us into places never planned
you are going far away with pieces of our lives

it will be short, it will take all your breath
it will not be simple, it will become your will

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Epitomes

Important Advances in Clinical Medicine

Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in radiology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Magnetic Resonance Imaging of Musculoskeletal Tumors

PRIMARY AND METASTATIC musculoskeletal tumors are common and potentially life-threatening. Although conventional radiographs are the primary means of detecting and diagnosing these tumors, plain films have two shortcomings—poor definition of tumor extension and poor detection of early osseous metastases. Magnetic resonance imaging (MRI), because it can produce images in multiple planes while displaying superior soft-tissue contrast resolution, has had a substantial effect on the description, preoperative staging, and postoperative follow-up of musculoskeletal tumors.

Several MRI findings increase a physician's index of suspicion for malignant tumor: inhomogeneous signal intensity, irregular margination, osseous destruction, encasement of neurovascular structures, and disruption of more than one compartment of bone, joint, or muscle. As a general rule, osseous and soft-tissue tumors have low or intermediate signal intensity on T1-weighted images and a high signal on T2-weighted images. Osteoblastic lesions are often the exception; they have low signal intensity on both T1- and T2-weighted images. Tumor conspicuity and delineation are usually not improved by administering intravenous gadolinium—gadolinium enhancement actually may obscure tumor margins.

The staging of musculoskeletal tumors requires determining the tumor extent, the histologic grade, and the presence or absence of metastases. A bone scan is the method of choice when screening the whole body for skeletal metastases, but its findings are notoriously nonspecific and its spatial resolution is so poor that precise preoperative planning is precluded. Computed tomography (CT), on the other hand, has good spatial resolution and effectively detects early cortical erosions, but its contrast resolution is inferior to that of MRI. The present consensus is that MRI is superior to CT for defining the infiltration of the tumor into bones, muscles, joints, and neurovascular structures. Tumor margins visualized by MRI have been shown to match closely those found by pathologic examination. At times, however, differentiating tumor from peritumoral edema is just as difficult with MRI as it is with other modalities, such as CT. Delineating tumor from healthy tissue is crucial for management and prognosis. In the case of osteogenic sarcoma, for example, MRI not only helps physicians plan an approach for biopsy and surgical procedures, it also helps them plan whether surgical intervention will consist of a limb-salvage procedure, an amputation, or a disarticulation.

Another important contribution of MRI is the monitoring of a tumor's response to adjuvant therapy—both preoperatively and postoperatively. Tumors responding to radiation or chemotherapy generally become more sharply marginated and decrease in size and vascularity.

Magnetic resonance imaging effectively helps characterize, stage, and follow musculoskeletal tumors and now is accepted as the imaging study of choice for such tumors.

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Vena Cava Filters

WHILE MOST PATIENTS with deep vein thrombosis can be successfully treated with anticoagulation therapy alone, some require the placement of an inferior vena cava filter, either as an alternative form of treatment or as adjunctive treatment along with anticoagulation, for prevention of pulmonary embolism. Generally accepted indications for placement of a vena cava filter include: absolute contraindication to anticoagulation; a complication of anticoagulation (such as hemorrhage); a relative contraindication to anticoagulation, such as patients prone to falling; the presence of a large amount of free-floating clot; short-term contraindications to anticoagulation, such as brain biopsy; deep vein thrombosis with unsuspected pulmonary embolism diagnosed at presentation; and a massive pulmonary embolism with residual lower extremity deep vein thrombosis. Since placement of a

vena cava filter does not treat the underlying deep vein thrombosis and anticoagulation alone does not protect against pulmonary embolism in patients with a large volume of free-floating clot, both anticoagulation therapy and vena cava filter placement are indicated in some patients.

The stainless steel Greenfield filter, in use for about 15 years, has traditionally been placed by surgical cutdown. Over the last several years, percutaneous placement by interventional radiologists has been increasing in popularity. Also, four other vena cava filters are now available. All are designed for percutaneous placement under local anesthesia without a surgical cutdown. They are placed most often via the right common femoral vein, but not uncommonly via the right internal jugular vein. Alternate sites include the left common femoral vein and, for the Simon nitinol filter, the antecubital vein. The location of the renal veins and the diameter of the inferior vena cava are determined by venography before filter insertion.

The ideal vena cava filter should be a device that is easily and safely placed percutaneously, biocompatible, mechanically stable, and able to trap threatening emboli while not causing occlusion of the vena cava. With the stainless steel Greenfield filter, the rates of vena cava occlusion and of recurrent pulmonary embolism appear to be about 5%. When placed properly, this filter very rarely migrates. The outer diameter of the introducer sheath is 29.5 F, so the vein at the entry site must be dilated to about 10 mm to accommodate the introducer. The filter is ferromagnetic and can cause artifacts on magnetic resonance images, totally obscuring or distorting the appearance of adjacent structures in the spine, retroperitoneum, or abdomen.

Several vena cava filters recently have undergone clinical trials in the United States and Europe. Most of the efforts in the design of these new filters have been directed towards producing an effective filter that can be placed through a smaller introducer. Although accurate data in large numbers of patients are not available, the vena cava patency rate and recurrent pulmonary embolism rate for these new filters appear to be similar to those reported for the stainless steel Greenfield filter. The titanium Greenfield filter, Vena Tech filter, and Simon nitinol filter are nonferromagnetic, causing little or no artifacts on magnetic resonance images. An advantage of the bird's nest filter is that it can be placed into large venae cava, up to 40 mm in diameter. The Simon nitinol filter is delivered with a relatively flexible 7 F catheter, so it can be placed via an antecubital vein.

While there is probably no single "best" vena cava filter, many options are now available to the interventional radiologist. Percutaneous placement of inferior vena cava filters, when done by physicians skilled in fluoroscopically monitored catheter and guide wire techniques, including performance and interpretation of vena cavagrams, is a relatively safe procedure. These filters clearly have a role in preventing pulmonary embolism.

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Pelvic Magnetic Resonance Imaging

ULTRASONOGRAPHY IS the established screening method for evaluating the pelvis and is often the only radiographic study needed for patients with pelvic disease. As techniques continue to be refined, however, there are now several clinical indications when magnetic resonance imaging (MRI) may give more information.

Magnetic resonance imaging has been shown to be superior to both ultrasonography and computed tomography in the staging of tumors arising from the endometrium or cervix. Recent studies have shown that administering gadolinium-labeled pentetate frequently may aid in evaluating the extent of spread of endometrial tumors and, occasionally, in the staging of more advanced cervical lesions.

Leiomyomas have a characteristic appearance on MRI, and although ultrasound can diagnose them easily, when infertility patients are to undergo myomectomy procedures, MRI can better define the number and location of leiomyomas. This enables the surgeon to have a detailed preoperative map of the lesions present. Magnetic resonance can also be used in the follow-up of patients who are receiving therapy with gonadotropin analogues for leiomyoma shrinkage.

When women present with a pelvic mass during pregnancy, MRI can be very useful in defining the nature and extent of the mass, thereby differentiating uterine leiomyomas (which can be observed during pregnancy) from adnexal masses (which may have to be removed).

Magnetic resonance imaging now is used more frequently in evaluating all types of congenital anomalies of the pelvis. Although its role in evaluating uterine (Mullerian duct) anomalies has been established for some time, it can also be used to define the abnormal anatomy present in infants with ambiguous genitalia. In neonates with anal atresia, MRI can define accurately the level of the obstruction, thereby helping to determine the type of surgical procedure that should be done and, at the same time, indicate possible associated anomalies of the kidneys and spine.

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Magnetic Resonance Angiography in the Head and Neck

MAGNETIC RESONANCE ANGIOGRAPHY (MRA) is an exciting application of magnetic resonance imaging. This technique creates a large number of thin, contiguous slices that can be viewed individually or reconstructed into a slab of images that are collapsed into a three-dimensional projection. These collapsed images allow the visualization of entire vessels. A cine loop may be obtained from a series of rotated MRA images in order to evaluate vascular anatomy rapidly. Choosing the best imaging parameters and the plane of imaging determines the success rate of this procedure.

Magnetic resonance angiography is a useful tool for evaluating patients with cerebral ischemia and stroke and for demonstrating occlusive disease in the cervicocranial, intracranial carotid, and vertebrobasilar circulations. Nearly all

arterial stenoses can be shown well, although typically they are overgraded. Magnetic resonance angiography examinations can be used to show the whole length of the carotid and vertebral vessels from their origins in the neck to their intracranial branches. Occlusive lesions of the intracranial arteries may also be identified, provided the vessels are of sufficient caliber and the intracranial vasculature is depicted.

Magnetic resonance angiography is ideal for placing an arterial occlusive lesion into one of three diagnostic groups—normal; minor stenosis of a vessel not impeding flow; or severe flow-limiting stenosis. These categories will indicate whether or not a patient needs to undergo conventional angiography or whether medical treatment is indicated.

Carotid ulcerations may not be detected with MRA because the relative stasis of blood within these lesions fails to produce adequate blood flow contrast. In such cases, duplex sonography of the carotid bifurcation can be useful. On the other hand, MRA can show the whole length of the internal carotid artery, which sonography is generally unable to do because of the mandible and skull base. Another pitfall of MRA relates to the overgrading of vascular stenoses. This error is produced by the presence of turbulent flow distal to the stenoses, which results in signal loss caused by dephasing.

The current application of MRA in intracranial aneurysms is limited to certain clinical situations such as evaluating patients with severe pulsating headaches or ocular migraine headaches. Magnetic resonance angiography can be used as a noninvasive screening examination in patients with a family history of or a phobia about aneurysms. Patients with subarachnoid hemorrhage must undergo a conventional angiogram. Magnetic resonance angiography has proven to be a good method of detecting and characterizing intracranial arteriovenous malformations. A variety of techniques have been used to delineate the nidus and major feeding vessels of these malformations.

Displacement or compression of vessels is another use of MRA in evaluating patients with intracranial tumors. The direction of displacement of a vessel can aid in deciding the proper surgical approach and in anticipating the structures as they are surgically identified. A neoplasm encasing a vascular structure can also be clearly depicted. Such encasement may involve either an arterial structure or the cortical veins and dural sinuses.

Magnetic resonance angiography is a useful technique for providing information about the intra- and extracranial carotid and vertebrobasilar circulations. When used in conjunction with the history and clinical findings, it can help physicians diagnose and treat patients with occlusive vascular diseases. Magnetic resonance angiography cannot substitute for conventional angiography in all cases and is not generally indicated in patients with subarachnoid hemorrhage.

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Intraoperative Radiotherapy

In clinical radiotherapy, higher doses of radiation increase the probability of tumor cure at the expense of normal tissue. Intraoperative radiotherapy offers a means to irradiate the tumor selectively, thus improving the therapeutic ratio. Intraoperative radiotherapy allows more precise localization of the target volume under direct vision while protecting normal tissue by manual displacement or shielding. Intraoperative radiotherapy also takes advantage of the increased biologic effect of a large single dose of radiation.

Typically, following diagnosis and staging by a multidisciplinary team, patients receive a moderate dose preoperatively of external beam irradiation (45 to 50 gray for 4½ weeks to 5 weeks) to a relatively large area, including the tumor and regions of suspected subclinical extension. After a break of about four weeks, the tumor is resected, if possible, and intestinal or biliary bypasses are done, if needed. At this point, the surgeon and radiation oncologist jointly determine the areas at greatest risk for recurrence, and those areas receive a single large fraction (10 gray to 20 gray) of intraoperative radiotherapy. The patient can be treated under anesthetic either in the operating room or the radiation therapy department.

The most promising uses for intraoperative radiotherapy are in gastric and rectal cancer. Data from studies in Japan indicate improvement in survival rates following surgical procedures and intraoperative radiotherapy in gastric tumors, compared with resection alone. The benefit is greatest in higher stage tumors. Data from this country show improved local control and survival in initially unresectable rectal carcinomas when intraoperative radiotherapy is added to preoperative irradiation and resection. Other sites where this therapy has shown promise include retroperitoneal sarcomas, mediastinal tumors, and biliary tumors. Toxicity has been minimal, and extensive data from studies in large animals detail the sensitivities of a wide range of tissues and organs to single large radiation fractions.

Intraoperative radiotherapy offers the possibility of improved local tumor control, which may increase the probability of tumor cure.

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Infections in Emergency Medicine—Newer Imaging Strategies

Infections are a common problem in emergency medicine. Newer imaging methods may expand the role of emergency radiology in the preliminary evaluation of some infectious and inflammatory processes.

Acute sinusitis can be evaluated with a limited sinus computed tomographic (CT) scan using 5 mm axial sections without contrast—one through the frontal sinuses, a second through the sphenoid-ethmoid level, and two through the maxillary sinuses. Sinus opacification, air-fluid levels, osse-

ous changes, and polypoid lesions are easily seen in under ten minutes. If more serious conditions are suggested, the patient can have an elective complete CT sinus study, but limited CT is more useful and no more costly than plain films.

Normal appendices are found in 15% to 25% of appendectomies for suspected acute appendicitis. Although deaths are rare, the morbidity and cost of negative laparotomy are substantial. Those in whom improved preoperative diagnosis is of particular value include women of reproductive age, where the normal appendix rate is 35% to 45%; pregnant patients where abortion is a consideration; very young, older, immunosuppressed, and other patients with atypical presentations.

Graded compression sonography, combined with transabdominal or transvaginal ultrasound, can visualize an abnormal appendix directly and show an alternative pathologic process, particularly gynecologic disease. In this study, the operator uses the transducer to gradually compress the abdomen at the site of pain, while searching for a dilated, thick-walled appendix, abnormal fluid collection, or appendicolith. Accuracies of 80% to 90% have been reported, but the method is operator dependent, and sensitivity is reduced if the appendix has perforated. Computed tomography may also show an abnormal appendix and is particularly useful in the 5% of patients who present with right lower quadrant mass, often distinguishing between phlegmon and abscess and helping with percutaneous drainage of the latter.

Patients with acute osteomyelitis usually do not have findings on plain radiographs seven to ten days after the onset of symptoms. Nuclear medicine technetium 99m (^{99m}Tc)-MDP bone scans are 95% sensitive but are not specific. A negative study result 24 hours after the onset of symptoms, however, essentially rules out acute bone infection. The three-phase bone scan improves specificity, often differentiating osteomyelitis from cellulitis, a common problem in the feet of diabetic patients. Specificity is further increased by the use of indium 111-labeled oxine or ^{99m}Tc-HMPAO leukocyte scans in conjunction with bone scans, but these scans take 24 hours to complete.

Magnetic resonance imaging (MRI) is as sensitive as and more specific than ^{99m}Tc-labeled medronate disodium bone scintigraphy, showing marrow as well as soft-tissue and periosteal changes. It can be done in less than two hours, but it is costly, not universally available, and, like bone scans, can occasionally result in false-positive results, particularly in the setting of trauma, previous surgical procedures, or neuropathic joint disease. In suspected vertebral osteomyelitis, however, MRI is the method of choice. Multiplanar imaging capabilities facilitate the depiction by MRI of vertebral body marrow alterations, disc involvement, and paraspinal or epidural abscess with unsurpassed clarity.

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Picture Archiving and Communication Systems

WITH THE INTRODUCTION of computed tomography (CT) and magnetic resonance imaging (MRI), an ever-increasing proportion of procedures done in radiology are acquired in a digital format. In addition, computed radiography (CR), which uses phosphostimulable plates instead of film, may replace conventional radiography, especially for portable examinations of the chest.

Picture archiving and communication systems (PACS) acquire, transmit, store, and display image information. Besides acquiring images directly from digital modalities (CT, MRI, and nuclear medicine) and from CR, these systems use laser digitizers to convert images on radiographic film to digital images. The images stored in PACS can be reproduced either on film with a laser camera or displayed using a high-resolution television monitor. Picture archiving and communication systems are expected eventually to replace most radiographic film. Reducing the operating costs associated with handling and storing radiographs and eliminating film and film processing may make these systems cost-effective in spite of the initial large expenditures for equipment.

When images are in digital form, they can be manipulated or processed by using window and level controls (intensity and contrast), inverse intensity (white on black to black on white), or edge-enhancement (unsharp masking). For a particular patient, images from the various modalities or from previous studies can be placed on the same or associated monitors for comparison. Such systems obviously would speed the retrieval and display of images. Treatment can be initiated earlier for patients in an Intensive Care Unit when digital images are readily available. The frequency of communication between the radiologist and the referring physician may decline, however, because in some instances the images are being viewed before the radiologist's interpretation is received.

The spatial and contrast resolution of the current digital modalities can be faithfully reproduced with PACS, especially if film is used for the primary interpretation. Although most investigators would agree that soft-copy display is also more than adequate, there still are concerns about the contrast gray levels that can be seen without varying the window and level on these displays. The simultaneous display of a large number of images is difficult. Also, subtle bone abnormalities, microcalcifications in mammography, and perhaps pneumothoraces are still somewhat difficult to see on these displays.

To date, only a handful of large institutions have successfully implemented clinical PACS. The reasons for the slow introduction of this technology are multiple, but two issues are clearly paramount: capital expense and resolution limitations. In one study examining the cost of PACS, the potential for substantial reductions in operating costs to offset capital depreciation was shown. This study, however, did not include a commercial manufacturer's cost for research and development, liability insurance, or a profit margin. Almost all of the savings that can be realized with PACS are related to the current digital modalities with little, if any, savings to be accrued on the general radiographic side (CR or digitizing radiographs).

In addition to the possible reduction in operating costs and improved efficiency in the handling of medical images,

PACS could enhance medical education by providing sophisticated retrieval capability from the image database based on radiologic or pathologic findings.

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Shoulder Magnetic Resonance Imaging

THE STRENGTH AND STABILITY of the most mobile but least stable joint in the body, the glenohumeral joint, is provided by the four muscles of the rotator cuff. The supraspinatus, infraspinatus, teres minor, and subscapularis muscles form a musculotendinous cuff that envelopes the humeral head and glenohumeral joint. The supraspinatus muscle is interposed between the humeral head and coracoacromial arch.

The impingement syndrome is a common cause of shoulder pain and may cause 95% of rotator cuff tears. When the soft tissue structures of the rotator cuff become entrapped between the coracoacromial arch and the greater tuberosity of the proximal humerus during abduction and elevation of the arm, a series of pathologic events may occur. Subacromial bursitis and rotator cuff tendinitis occur first with progression to fibrosis and rupture of the rotator cuff later. The impingement may occur at the site of the anterior acromion, at the acromioclavicular joint due to spurring, or along the undersurface of the coracoacromial ligament.

Most rotator cuff tears affect the supraspinatus tendon 1 cm proximal to its site of insertion, the "critical zone," near its attachment to the humeral tuberosity. Anterior and posterior extensions may occur, but less frequently. Complete tears are defined as full thickness tears of the rotator cuff. Partial tears are incomplete tears that do not allow fluid to flow between the glenohumeral joint and the subacromial bursa.

The signs and symptoms of rotator cuff tears are not specific. Consequently, the diagnosis is often delayed until a complete tear has occurred. The goal of evaluating shoulder pain should be to determine the cause before irreversible tendon damage has occurred.

Magnetic resonance imaging (MRI) provides excellent depiction of the anatomic structures of the shoulder, including the rotator cuff, the long head of the biceps tendon, articular capsule, muscles, and bone. The improved contrast and additional imaging planes of MRI provide the orthopedic surgeon with anatomic information regarding the presence of tendinitis versus a partial tear versus a complete tear of the rotator cuff. This information, in addition to the clinical presentation, assists the surgeon in determining treatment, that is, physical therapy, arthroscopy, or an open surgical procedure.

The MRI findings of tendinitis are thickening of the cuff tendon and intermediate (grey) signal replacing the normal low signal (black) tendon. Partial tears show a focal thinning of the tendon and may have fluid within the niche. With complete rotator cuff tears, the normal low-intensity signal of the tendons is interrupted by a bright signal indicating discontinuity of the rotator cuff. The (high signal) discontinuity may be filled by either fluid, granulation tissue, or hypertrophied synovium.

Compared with arthroscopy, MRI showed a sensitivity of 100% and specificity of 88% in evaluating rotator cuff tears and a sensitivity of 92% and a specificity of 100% compared to a surgical procedure. Magnetic resonance imaging is able to show bony impingement on the rotator cuff tendon and can indicate other causes of shoulder pain, including effusions, occult fractures, metastases, avascular necrosis, labral tears, and loose bodies. Magnetic resonance gadolinium arthrography may be indicated in cases of dynamic instability, failed surgical procedures for rotator cuff tears, negative noncontrast MRI, and in differentiating partial tears from tendinitis.

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The Imaging of Impotence

IMPOTENCE AFFECTS more than 10 million men in the United States. Clinical evaluation usually can exclude endocrinologic imbalance, neurogenic dysfunction, and psychologic problems as etiology. A patient who fails to get an erection after vasoactive medications are injected probably has hemodynamic impotence. Dynamic studies that include imaging techniques are now available to discriminate between arterial and venous pathology.

Doppler ultrasound with color flow and spectral analysis, dynamic infusion corpus cavernosometry and cavernosography, and selective internal pudendal arteriography are outpatient diagnostic procedures that will differentiate, image, and quantify the abnormalities in patients with hemodynamic impotence. Not all tests are needed in every patient. Each of these examinations is preceded with the intracavernosal injection of vasoactive medication. Papaverine hydrochloride, phentolamine mesylate, or prostaglandin E_1 will overcome normal sympathetic tone and produce an erection by smooth muscle relaxation and arterial dilatation in a normal patient.

Color-flow Doppler and spectral analysis will show the cavernosal arteries and can identify the hemodynamic effects of stricture or occlusion. Peak systolic velocity is measured. Normal ranges are well established. Spectral analysis also is used to predict the presence of venous disease. Sizable venous leaks in the dorsal penile vein are readily imaged. While the technique may not adequately identify low-grade venous pathology, it will identify the size and location of fibrous plaque formation associated with Peyronie's disease.

Cavernosography or cavernosometry is a separate procedure that will quantitate the severity of venous incompetence as well as specifically identify the various avenues of systemic venous return that must be localized if venous occlusive therapy is chosen. In this study, the peak arterial systolic occlusion pressure is quantified during erection, and the presence of arterial pathology can be confirmed. The arterial data are not as reliable as the ultrasound-obtained data because they rely on audible Doppler, which can be obscured in the underlying "noise" heard with erection. The arterial data obtained with both of these examinations are quantitative and replace the qualitative audible Doppler used previously. Specialized equipment (Life Tech, Houston, Texas) allows dy-

namic data acquisition, ensuring that the needed information is obtained at peak stimulation.

Arteriography is done only if reconstructive surgery is contemplated. The examination includes subselective catheterization of the internal pudendal arteries, magnification technique, and evaluation of the recurrent epigastric arteries, which will be harvested for revascularization. An arterial operation is usually successful in younger patients with perineal trauma with a single point of stenosis or occlusion but has been least successful in those patients with atherosclerosis because of the multifocal nature of this disease.

Diagnostic information available today is more specific and reliable than at any time in the past and can realistically estimate the severity of the hemodynamic disorder and allow individual treatment options. Ongoing studies will show whether the data these studies provide make an important difference in the treatment of vascular impotence.

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Current Status of Discography

Discography is a physiologic evaluation of intervertebral discs consisting of volumetric, manometric, pain provocative, and radiographic appearance. Since its introduction in 1948, discography has gained and lost popularity several times. It suffered a major setback in 1968, after reports of 37% false-positive results in normal volunteers. The literature is still replete with articles that have reported its many advantages and applications and have considered it an essential guide to planning operations on the spine.

The procedure consists of injecting contrast material under fluoroscopic control via an extradural or intradural approach. The injection in a normal disc is painless—the patient feels only a pressure sensation—and the contrast agent remains in the nucleus pulposus. The test result typically is considered positive when injection creates pain that simulates the patient's symptoms and is associated with an abnormal morphologic discogram appearance or contrast extravasation, or both. An 89% parallel correlation of magnetic resonance imaging and discography has been reported.

Discography is indicated when magnetic resonance imaging, computed tomography, or a myelogram shows negative or equivocal findings for disc disease; when there is a positive result on these tests indicating disc disease at multiple levels—in this case, discograms are used to determine the symptomatic level or levels; in the case of recurrent low back pain after a surgical procedure to distinguish scar tissue from recurrent disc herniation; to evaluate the discs above or below the proposed spinal fusion; and as a test for an injection of cortisone.

Although discography is a relatively safe procedure, a discitis rate of 1% to 4% has been reported. Allergic reactions to nonionic contrast agents are uncommon, and epidural abscess is extremely rare. The total cost for a three-disc-level procedure is currently between $1,000 and $2,000, including professional and hospital fees. Despite the clouds of controversy surrounding discography, it remains the only provocative test available and is indicated as a complementary test before a surgical procedure is done on the spine.

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Radiosurgery for Tumors and Arteriovenous Malformations of the Brain

Tumors and arteriovenous malformations located in deep, inaccessible areas of the brain are now treatable with radiosurgery, a technique that uses high doses of radiation to inactivate these lesions. Several different methods of radiosurgery have been developed, but all share the common characteristic of focusing multiple, precise, small radiation beams on an intracranial target. Although charged particle beams have been successfully developed for radiosurgery, the most widely available devices use photon radiation generated by a linear accelerator or a multiple cobalt 60 source machine ("Gamma Knife").

Radiosurgery is given in a single or a very small number of treatments, unlike conventional radiotherapy in which multiple fractions are delivered over a period of weeks. To do radiosurgery, a stereotactic localization device is fixed to the patient's skull; this apparatus provides a coordinate system for defining the position of the lesion and its relationship to surrounding brain structures. Computed tomography scans are done to determine the three-dimensional configuration of the lesion; angiography and magnetic resonance scans may also be useful. Computed radiation treatment planning is used to design radiation dose distributions that conform to the shape of the target, confining the areas of high dosage to the lesion, with less irradiation of surrounding brain tissue. Radiosurgery is done—usually on an outpatient basis—with the patient's head immobilized in the localization device.

Excellent results have been obtained using radiosurgery for patients with inoperable arteriovenous malformations. Most treated with radiosurgery—60% to 90%—are completely obliterated as documented by follow-up angiography. The risk of cerebral hemorrhage is eliminated provided the malformation is totally obliterated. Regression of the lesion is slow after radiosurgery, however, taking one to three years to complete. The risk of bleeding persists during the interval between treatment and complete obliteration. Radiosurgery can be used as the sole modality to treat small arteriovenous malformations—less than 3 cm—or can be combined with angiographic embolization for more extensive lesions.

A variety of benign and malignant brain tumors have been treated with radiosurgery, including acoustic neuromas, meningiomas, pineal and pituitary region tumors, gliomas, posterior fossa neoplasms and metastatic lesions. For selected small, noninvasive tumors, radiosurgery alone may be used, while for larger neoplasms, surgical debulking can be ini-

tially used, followed by radiosurgery to treat the residual tumor. Radiosurgery is particularly useful for tumors that have recurred after a surgical procedure and conventional radiation therapy, provided the volume of recurrent disease is small.

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Chemoembolization in the Treatment of Hepatic Malignancy

UNRESECTABLE HEPATIC MALIGNANCY, either primary or metastatic, carries a grave prognosis, with a usual life expectancy of three months to six months, and, unfortunately, the condition is common. Colon carcinoma, which frequently spreads to the liver, will take 60,000 American lives every year. Hepatocellular carcinoma (HCC), the most common fatal malignancy worldwide, is endemic in the Orient. With Pacific Rim migration, the incidence is expected to increase in the western United States. Response rates with systemic chemotherapy are about 30% and, in hepatic metastases caused by colon carcinoma, about 20%.

The poor prognosis and high prevalence have led to innovative treatments of liver tumors, including infusing chemotherapy directly into the hepatic artery (to increase the concentration delivered to the tumor) and blocking the blood supply with microscopic particles (to cause tumor ischemia). Chemoembolization is a combination of the two therapies in which chemotherapy and particles are infused simultaneously.

Three congruent circumstances permit the safe and effective application of such regional treatments: the liver has a dual blood supply with either the hepatic artery or portal vein capable of sustaining the organ; tumors of the liver are supplied by the hepatic artery; and the hepatic artery is nearly always accessible percutaneously with current catheterization techniques.

Patients eligible for chemoembolization include those in whom the tumor is unresectable yet confined to the liver. Initially, angiography of the celiac axis and superior mesenteric artery are done to determine the blood supply of the liver and status of the portal vein. A small (2F to 3F) catheter is placed coaxially through the larger (5F to 6F) guiding catheter past the intestinal and gallbladder vessels into the hepatic artery. The chemoembolization mixture is infused while monitored by fluoroscopy. Nausea and pain after the procedure are greatly relieved by the antiemetic ondansetron and intra-arterial lidocaine, respectively. Complications such as embolization of the intestine, hepatic abscess, or infarction occur in less than 3% of patients. Response rates in hepatocellular carcinoma have ranged from 50% to 75%. In addition, most recent studies have involved patients who failed to respond to systemic chemotherapy.

Newer applications and broader use of hepatic chemoembolization are expected. Such advances may include the shrinkage of hepatic malignancies permitting curative resection, palliation until liver transplantation, safe use in patients with portal vein thrombosis, and the application in children with hepatoblastoma and hepatocellular carcinoma.

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Vasodilator and Exercise Cardiac Perfusion Scintigraphy

THE LONG ANTICIPATED Food and Drug Administration approval of two technetium 99m (^{99m}Tc)-based cardiac perfusion imaging agents and the coronary vasodilator dipyridamole for intravenous administration occurred early in 1991.

Dipyridamole increases coronary blood flow without exercise and improves the sensitivity of isotope imaging in those patients unable to exercise well. Side effects such as chest pain, headache, and dizziness are common but reversible with aminophylline.

The two ^{99m}Tc isonitrile agents differ greatly in biodistribution. The ^{99m}Tc-teboroxeme redistributes rapidly from myocardium. This has advantages for rapid sequential stress and rest imaging but demands rapid imaging following exercise. Ideally, the exercise is done in close proximity to a multi-head single photon emission computed tomography (SPECT) system.

The ^{99m}Tc-sestamibi agent remains fixed for hours in the myocardium proportional to regional blood flow at the time of injection. This has distinct logistic advantages. The physical distance of the laboratory from the nuclear medicine site or delays in completing examinations no longer compromise the study as they might with thallium 201 (^{201}Tl). The ^{99m}Tc not only reflects perfusion but also shows myocardial viability better than ^{201}Tl. Areas of ischemia appearing as infarcts are less common.

Both ^{99m}Tc compounds have distinct physical advantages over ^{201}Tl. The 140 kiloelectron volt (keV) photons are less attenuated by tissue and better suited for SPECT imaging than ^{201}Tl (80 keV). The shorter half-life—6 hours versus 73 hours—allows more activity with less radiation absorbed. Initial reports indicate comparable or favorable results compared with ^{201}Tl, and further experience is likely to show improved results as the physical advantages are exploited by changing techniques. Cost is comparable and may even be less per study in high-volume departments.

Positron studies have distinct physical advantages over all SPECT agents. With very high-energy (511 keV), short-lived isotopes, attenuation by tissue is minimal and specificity is higher than SPECT. Combined perfusion and glucose metabolism are the gold standard for noninvasive assessment of viability. The high cost and limited availability are major disadvantages.

As the physical advantages of the ^{99m}Tc compounds are exploited to improve the specificity of SPECT imaging, they will have an important effect on the evaluation of coronary

disease by scintigraphy. Vasodilator infusion has already improved scintigraphy results in those unable to exercise well.

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The Simplicity and Safety of Radiologically Placed Gastric Tubes

ENDOSCOPISTS AND, MORE RECENTLY, radiologists have shown that successful gastric intubation, once strictly a surgical procedure, can be done outside the operating room without an incision.

The procedure is done with a fluoroscope while the patient is fully awake. The stomach is inflated with air via a nasogastric tube, which pushes the transverse colon away from the abdominal wall. An appropriate site on the skin surface is prepared and then anesthetized with local anesthesia. For patients in whom a nasogastric tube cannot be passed, the stomach can be inflated through a skinny needle placed percutaneously into the stomach bubble. Under fluoroscopic guidance, a needle is inserted into the gastric lumen through which a guide wire is placed. The needle is removed and the tract is dilated to the desired width (usually 12 F to 16 F). A feeding tube, which usually has some form of anchor, such as a self-retaining pigtail loop, is then inserted. Some prefer to secure the stomach to the abdominal wall using small T-anchors introduced through separate needle punctures, but we have found that unnecessary.

An advantage of radiologic guidance is that ultrasound can be used to locate the spleen or liver should they be near the proposed entry site, and the colon can be quickly filled with air or contrast material if it is difficult to see with the fluoroscope. If or when a jejunal tube is needed, then the G-tube is readily replaced with a longer tube that is fluoroscopically guided into the small bowel. After bowel sounds return, usually within 24 hours, the tube is then ready to be used for feedings. The procedure usually takes under 30 minutes to do, and, if the tube should stop working after the tract matures—usually by two to four weeks—it is easily exchanged in a few minutes over a guide wire on an outpatient basis.

Because of the distended stomach, air can escape into the peritoneal cavity, which is rarely, if ever, of any clinical consequence. Morbidity and mortality data show that fluoroscopically directed feeding tubes can be placed with the same, and perhaps fewer, complications than surgically or endoscopically placed tubes. That, with the added benefits of no anesthesia or operating room charges, makes the radiologically placed feeding tube an attractive alternative for patients in need of enteral nutrition.

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Alerts, Notices, and Case Reports

The Sulfone Syndrome in a Patient Receiving Dapsone Prophylaxis for *Pneumocystis carinii* Pneumonia

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DAPSONE IS A DIAMINOPHENYL sulfone indicated for the treatment of leprosy, to prevent malaria in travelers to endemic regions, and to treat several dermatologic conditions, including dermatitis herpetiformis. Dapsone interferes with the production of folate from para-aminobenzoic acid (PABA). Because PABA is the main substrate for folate synthesis by *Pneumocystis carinii*, dapsone is used in the treatment of and prophylaxis against *P carinii* pneumonia in patients infected with the human immunodeficiency virus type 1.[1-4]

Common side effects of dapsone therapy include the development of abnormal serum aminotransferase levels and hemolysis in patients deficient in glucose-6-phosphate dehydrogenase (G6PD).[5] A severe dapsone hypersensitivity syndrome, also known as the sulfone syndrome, has been reported sporadically in the literature. This is characterized by fever, rash, hemolytic anemia, atypical lymphocytosis, and acute (rarely fulminant) hepatic injury.[6] We report a case of the sulfone syndrome in a patient with the acquired immunodeficiency syndrome (AIDS) who was receiving dapsone as primary prophylaxis against *P carinii* pneumonia.

Report of a Case

The patient, a 35-year-old homosexual man with AIDS, was admitted to Stanford University Hospital with nausea, vomiting, and jaundice. He had been diagnosed with Kaposi's sarcoma eight weeks before admission based on the results of a biopsy of violaceous lesions on his legs. The patient was being treated with trimethoprim-sulfamethoxazole as prophylaxis against *P carinii* pneumonia. In retrospect, the patient had noted a coated tongue, fevers, night sweats, and the skin lesions on his legs for a year. Six weeks before admission, he was randomly assigned to the dapsone treatment arm of a *P carinii* pneumonia prophylaxis protocol, and trimethoprim-sulfamethoxazole was discontinued. He received 50 mg of dapsone orally twice a day and 200 mg of zidovudine orally five times per day. At the time of study entry, his laboratory tests revealed a hemoglobin level of 140 grams per liter (14 grams per dl), a hematocrit of 0.40 (40%), normal serum liver function test values, a G6PD activity of 45 minutes (normal 0 to 60 minutes), and a total T-helper lymphocyte count of 0.168×10^9 per liter (168 per μl).

He continued to have night sweats and occasional low-grade fevers after dapsone therapy was begun. Two weeks before admission his hemoglobin level was 103 grams per liter (10.3 grams per dl) and his hematocrit was 0.302 (30.2%). One week before admission, chills and fever to 40°C (104°F), anorexia, headache, nausea, dark urine, and diarrhea developed. Three days before admission he had a hematocrit of 0.24 (24%), a leukocyte count of 5.5×10^9 per liter (5,500 per μl), a bilirubin level of 63.27 μmol per liter (3.7 mg per dl), alkaline phosphatase 229 units per liter, aspartate aminotransferase 772 units per liter, alanine aminotransferase 650 units per liter, and lactate dehydrogenase 4,896 units per liter. The administration of dapsone and zidovudine was discontinued. Two days before admission his leukocyte count was 5.5×10^9 per liter, with 0.32 polymorphonuclear leukocytes, 0.04 band forms, 0.46 lymphocytes, and 0.10 reactive lymphocytes. He continued to have chills, sweats, and high fevers and in addition had dizziness with standing and shortness of breath with minimal exertion. He was admitted to Stanford University Medical Center for further evaluation.

The patient's history was notable for a positive hepatitis B surface antigen test. He had no history of blood transfusions, intravenous drug abuse, or alcoholism and no known drug allergies. He was taking no medications other than zidovudine and dapsone during the six weeks before being admitted to hospital.

On physical examination, he was jaundiced and appeared toxic. His temperature was 38.6°C (101.5°F), blood pressure 120/80 mm of mercury, pulse 80 per minute, and respirations 20 per minute. There were no orthostatic changes in blood pressure or pulse. Skin lesions consistent with Kaposi's sarcoma were noted on the lower extremities, the right groin, the soft palate, and the left side of the face. Scleral icterus was present. A funduscopic examination revealed cotton-wool spots bilaterally. The tongue was coated white, and there were small, mobile, tender anterior cervical and left axillary lymph nodes. The results of respiratory and cardiovascular examinations were normal. The abdomen was soft with normal bowel sounds; the right upper quadrant was tender to palpation. His liver measured 15 cm by percussion and was palpable 3 cm below the right costal margin. His spleen was palpable 2 cm below the left costal margin. Results of the genital, rectal, and neurologic examinations were normal.

Laboratory data on admission were significant for 2+ bilirubinuria. Testing resulted in a hemoglobin level of 79 grams per liter (7.9 grams per dl), a hematocrit of 0.238 (23.8%), a mean corpuscular volume of 122 fl, and a reticulocyte count of 37×10^{-3} (3.7%). The leukocyte count was 8.5×10^9 per liter (8,500 per μl), with 0.26 polymorphonu-

(Mohle-Boetani J, Akula SK, Holodniy M, Katzenstein D, Garcia G: The sulfone syndrome in a patient receiving dapsone prophylaxis for *Pneumocystis carinii* pneumonia. West J Med 1992 Mar; 156:303-306)

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
G6PD = glucose-6-phosphate dehydrogenase
PABA = para-aminobenzoic acid

clear leukocytes, 0.11 band forms, 0.44 lymphocytes, and 0.19 reactive lymphocytes. A peripheral smear showed numerous atypical lymphocytes, spherocytes, schistocytes, and macrocytes. Results of direct and indirect Coombs' tests were unremarkable. Haptoglobin measurement and a Heinz body preparation were not done. Levels of serum electrolytes, blood urea nitrogen, and creatinine were within normal limits. The total bilirubin level was 104.3 μmol per liter (6.1 mg per dl), with a direct-reacting bilirubin of 87.2 μmol per liter (5.1 mg per dl). Other laboratory values were alkaline phosphatase, 329 units per liter; alanine aminotransferase, 1,159 units per liter; aspartate aminotransferase, 1,099 units per liter; and lactate dehydrogenase, 4,961 units per liter. The serum albumin level was 37 grams per liter and the prothrombin time was 14.0 seconds.

A chest radiograph showed a normal cardiomediastinal silhouette and no parenchymal infiltrates. An abdominal ultrasonogram revealed a homogeneous liver without focal masses or biliary tract abnormalities but with splenomegaly. Assays revealed no antibodies to hepatitis A and D but did detect hepatitis B surface antigen and hepatitis B e antigen.

The patient was treated with intravenous ampicillin, gentamicin sulfate, and clindamycin; these were discontinued when blood cultures showed no growth after 48 hours. He received intravenous fluids and transfusions of packed erythrocytes. He did not receive corticosteroid treatment. He continued to have a high fever, and the aminotransferase abnormalities progressed over the first five hospital days. He developed a maculopapular rash on the trunk and extremities on the fourth hospital day, which was thought to be a reaction to treatment with intravenous ampicillin.

A liver biopsy done on the third hospital day revealed lobular and portal infiltrates with mononuclear and polymorphonuclear (predominantly eosinophilic) granulocytes; granulomas and eosinophilic bodies were present throughout the lobule (Figure 1). There was normal lobular architecture with no fibrosis or lobular collapse. No intranuclear or cytoplasmic inclusion bodies were identified.

The presence of infectious agents known to cause acute granulomatous hepatitis was ruled out by the following tests: serologic assays were negative for immunoglobulin M antibodies to cytomegalovirus; shell vial cultures were negative for cytomegalovirus; cultures of the liver biopsy specimen for bacterial, mycobacterial, fungal, and viral agents showed no growth; and peripheral blood cultures did not grow *Mycobacterium avium-intracellulare* or other pathogens.

The patient's fever, systemic symptoms, rash, and serum aminotransferase abnormalities resolved over 10 days (Figure 2), and the patient was discharged from the hospital. Two weeks after discharge his serum aminotransferase levels were nearly normal. Zidovudine was reinstituted at the previous dosage, and pentamidine 300 mg was given monthly by aerosolization. The patient has had no recurrence of hepatitis or anemia. He remains positive for hepatitis B surface antigen and hepatitis B e antigen.

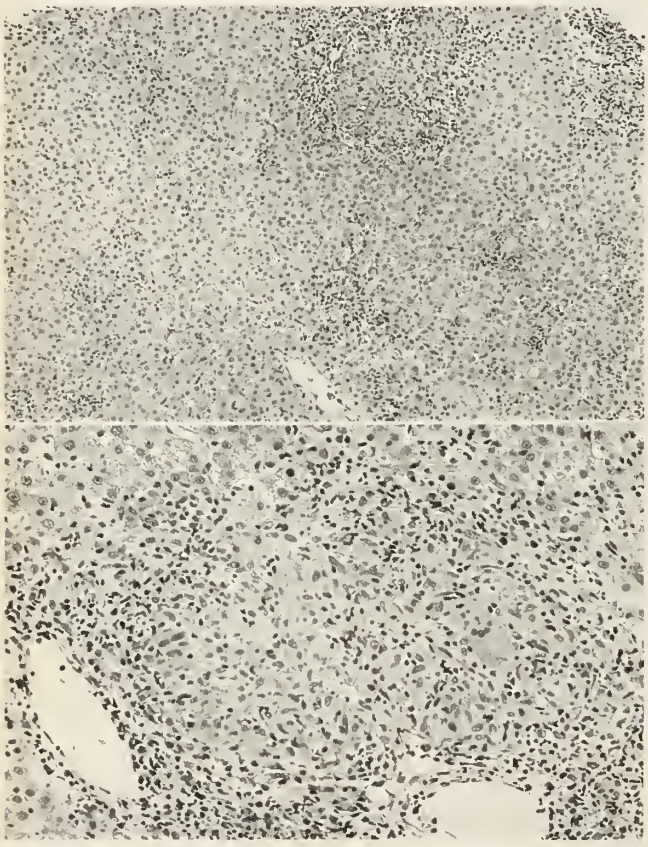

Figure 1.—Liver biopsy findings included **Top**, panlobular mixed mononuclear and polymorphonuclear infiltrate (hematoxylin and eosin stain; original magnification × 100) and **Bottom**, a well-formed portal granuloma with a giant cell (hematoxylin and eosin stain; original magnification × 200).

Discussion

This case illustrates that treatment with relatively low doses of dapsone can result in hemolytic anemia and the sulfone syndrome, even in patients with normal G6PD activity. Dapsone is metabolized to *N*-hydroxyl, diaminodiphenyl sulfone (NOH-DDS); this compound has a mild oxidant activity, and mild methemoglobinemia and hemolysis occur in most persons treated with dapsone. The hemolysis is accentuated, resulting in anemia in patients who are G6PD deficient and in those treated with high doses for prolonged periods.[5] Hemolysis has been reported independent of as

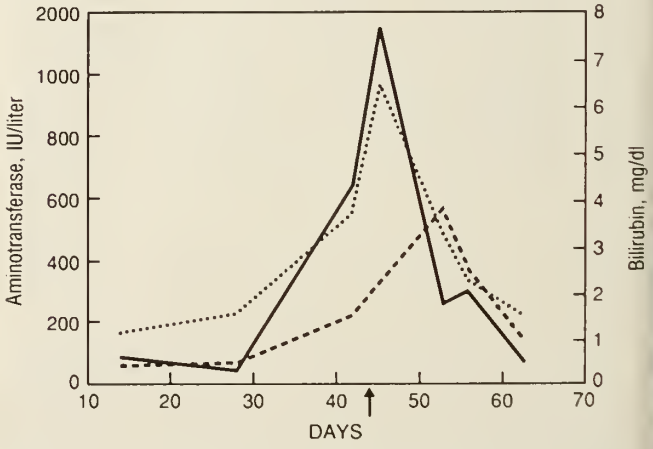

Figure 2.—The graph shows the time course of abnormal liver tests in the patient. ↑ = time of liver biopsy, — = ALT = alanine aminotransferase (normal 7 to 56 IU/liter), - - = alkaline phosphatase (normal 43 to 122 IU/liter), ··· = total bilirubin (normal 0.2 to 1.0 mg/dl).

well as coincident with the sulfone syndrome.[6] In the present case, there was a mild reduction of the hematocrit within the first two weeks of therapy. In the third week a dramatic hemolysis was seen coincident with the cholestatic hepatitis and fever, which resolved after treatment with dapsone was discontinued. The methemoglobin level was not measured.

A dapsone hypersensitivity syndrome was first alluded to by Lowe and Smith in 1949 when they noted a 2% incidence of exfoliative dermatitis among patients treated with dapsone for leprosy.[7] In the subsequent decade, the sulfone syndrome was described as a mononucleosis-like syndrome characterized by exfoliative dermatitis, hepatomegaly, jaundice, splenomegaly, lymphadenopathy, and a predominance of peripheral mononuclear cells in ten patients treated for less than two months with dapsone for leprosy[8,9] and in three malnourished patients who were treated for six weeks with dapsone for tuberculosis.[10] Liver biopsies in the patients with tuberculosis revealed extensive liver necrosis in one and focal necrosis in the other two.

Since the original description, there have been similar reports in patients who were treated with dapsone for leprosy[11] and for many dermatologic disorders.[6,12-16] The dosage of dapsone in these cases ranged between 50 and 300 mg per day. Four were receiving 100 mg or less of dapsone per day. With relatively low doses of oral dapsone in most of the cases, the serum concentrations achieved would likely be lower than those associated with hepatotoxicity. In addition, the findings of a peripheral blood mononuclear cell predominance—an exfoliative dermatitis and granuloma formation with eosinophilia—suggest a delayed hypersensitivity reaction. Therefore, the sulfone syndrome is most likely a hypersensitivity reaction rather than a toxic reaction.

TABLE 1.—*Summary of Published Cases of the Sulfone Syndrome*

Source	*Underlying Disease*	*Age and Sex of Cases*	*Dose of Dapsone, mg/day*	*Time to Onset After Dapsone Begun, wk*	*Clinical Features*	*Liver Abnormalities*	*Leukocyte Abnormalities*
Allday and Barnes, 1951[8]	Leprosy	7 cases: age and sex not available	100 × 2 wk, 200 thereafter	8	Fever, rash, hepatomegaly, lymphadenopathy	Not available	Increased lymphocytes or monocytes
Jelliffe, 1951[10]	Tuberculosis, malnutrition	3 cases: 2 men Girl, 7 y	100 × 1 wk, 200 × 1 wk, 300 thereafter	6	Fever, rash	Liver biopsy: necrosis	Not available
Leiker, 1956[9]	Leprosy	Woman, 25 y	100 twice/wk, increase by 100 each week	5	Fever, rash, splenomegaly, lymphadenopathy		All had increased lymphocytes or monocytes
		Man, 25 y		4	Fever, rash	Jaundice	
		Woman, 26 y		7	Fever, rash, splenomegaly, lymphadenopathy		
Potter et al, 1967[14]	Erythema elevatum diutinum	Man, 68 y	200	3-4	Rash, lymphadenopathy	Jaundice, hemolytic anemia	Increased lymphocytes or monocytes, atypical lymphocytosis
Millikan and Harrell, 1970[6]	Dermatitis herpetiformis	Man, 21 y	200	3	Fever	Abnormal liver function tests, hemolytic anemia	Both had increased lymphocytes or monocytes
		Man, 50 y	200	3	Fever	Jaundice, abnormal liver function tests, hemolytic anemia	
Frey et al, 1981[11]	Leprosy	Boy, 17 y	100	3	Fever, rash, hepatomegaly, splenomegaly, lymphadenopathy	Abnormal liver function tests, hemolytic anemia, jaundice	Increased lymphocytes or monocytes, atypical lymphocytosis
Tomecki and Catalano, 1981[15]	Acne vulgaris	Girl, 16 y	50	2	Fever, hepatomegaly, splenomegaly, lymphadenopathy	Abnormal liver function tests, jaundice, hemolytic anemia	Atypical lymphocytosis
Kromann et al, 1982[13]	Psoriasis	Woman, 33 y	100	2-3	Fever, rash, hepatomegaly, lymphadenopathy	Abnormal liver function tests, liver biopsy	Increased lymphocytes or monocytes, atypical lymphocytosis
Johnson et al, 1986[12]	Leukocytoclastic vasculitis	Woman, 49 y	50	2	Fever, rash, hepatomegaly	Abnormal liver function tests, hemolytic anemia	None
Lawrence et al, 1987[17]	Dermatitis herpetiformis	Woman, 19 y	50 increased to 150	3-4	--	Hemolytic anemia, jaundice, abnormal liver function tests	Not available
Wille and Morrow, 1988[16]	Brown recluse spider bite	Man, 55 y	100	3	Fever	Abnormal liver function tests	Increased lymphocytes or monocytes, atypical lymphocytosis

By reviewing the 21 reported cases,[6,8-17] we can make several generalizations concerning the sulfone syndrome:

- all cases occurred within two months of the patients' starting dapsone treatment;
- all patients had fever; and
- all but three patients had a rash and evidence of hepatic injury (hepatomegaly, jaundice, or hyperbilirubinemia).

There were 15 cases with lymphadenopathy and 6 cases with splenomegaly. A predominance of lymphocytes was reported in 15, and atypical lymphocytosis was noted in 4 cases. Hemolytic anemia was reported in 6 patients. Table 1 summarizes these case reports.

Our patient has the following features in common with other patients reported with the sulfone syndrome: onset of illness within two months of initiating treatment, fever, jaundice, hepatomegaly, lymphadenopathy, atypical lymphocytosis, hemolytic anemia, elevated aminotransferase levels, and a liver biopsy revealing granulomas with a panlobular eosinophilic infiltrate. Although the histologic differential diagnosis of granulomatous hepatitis is extensive,[18] our patient's clinical course was characteristic of an acute toxic injury, and the presence of a large number of eosinophils supports the histologic diagnosis of an allergic granulomatous reaction.[19] The presence of infectious agents known to cause acute granulomatous hepatitis was ruled out, no drug or toxic exposure was reported by the patient other than the use of zidovudine and dapsone, and subsequent challenge with zidovudine has not resulted in a recurrence of his hepatitis.

We think that this is the first report of the sulfone syndrome occurring in a patient with AIDS in whom *Pneumocystis carinii* pneumonia prophylaxis was the indication for dapsone use. The dose of dapsone used was relatively high, in accordance with the AIDS Cooperative Treatment Group 081 protocol, but the evidence suggests a hypersensitivity reaction rather than a dose-related adverse effect. Given the probable widespread use of dapsone for treating AIDS patients in the future, physicians should be alert for other cases of the sulfone syndrome.

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Odontoid Osteomyelitis

An Unusual Presentation of an Uncommon Disease

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OSTEOMYELITIS of the upper cervical vertebrae is rare. There have been few published reports, and these have stressed the difficulties inherent in making the diagnosis.[1-5] Virtually all patients have had some underlying chronic disorder, such as long-standing diabetes mellitus[2-4] or intravenous drug abuse.[5] We therefore report a case of odontoid osteomyelitis that occurred in a previously healthy person. The diagnosis in this patient was promptly made using magnetic resonance imaging (MRI). Although experience with this imaging technique in evaluating cases of suspected osteomyelitis is gradually expanding,[6-8] this is the first instance, to our knowledge, in which MRI has been applied in the diagnosis of cervical osteomyelitis.

Report of a Case

The patient, a 57-year-old man, was seen because he had had persistent neck pain, tactile fever, and sore throat for three weeks. The neck pain was not alleviated by local heat compresses or by taking ibuprofen. He was not given antibiotics. He had no history of surgical procedures or trauma of the neck and no evidence of underlying disease. Although he occasionally drank large amounts of alcohol, this had not caused medical problems, nor had it interfered with his work for 25 years as an aircraft assembler.

On physical examination, he was well developed and in no acute distress. His temperature was 37.9°C. The pharynx was swollen and edematous, and lateral movement of the neck was notably impaired. There were no other abnormal physical findings.

(Ruskin J, Shapiro S, McCombs M, Greenberg H, Helmer E: Odontoid osteomyelitis—An unusual presentation of an uncommon disease. West J Med 1992 Apr; 156:306-308)

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
MRI = magnetic resonance imaging

The leukocyte count was 17.6×10^9 per liter with 0.85 polymorphonuclear leukocytes and 0.15 lymphocytes. The hemoglobin level was 140 grams per liter (14 grams per dl), and the platelet count was 667×10^9 per liter. The erythrocyte sedimentation rate was 90 mm per hour. The blood urea nitrogen and creatinine levels and the results of tests of liver function were all within normal limits. Culture of blood specimens drawn on admission was sterile. Plain roentgenograms of the cervical spine showed no soft tissue or bony abnormality.

Magnetic resonance imaging (T1-weighted images with and without gadolinium enhancement) of the cervical spine revealed prevertebral and epidural soft tissue masses and abnormal signals in the odontoid bone marrow consistent with osteomyelitis (Figures 1 and 2). A computed tomographic (CT) scan also showed retropharyngeal soft tissue swelling, but osteomyelitic changes in the odontoid were not detected.

The presumptive retropharyngeal abscess seen on the MRI and CT scan was incised and drained, and 5 ml of pus was aspirated. Culture of specimens incubated aerobically grew *Staphylococcus aureus, Lactobacillus casei,* and *Lactobacillus fermentum.* Anaerobic cultures were inadvertently

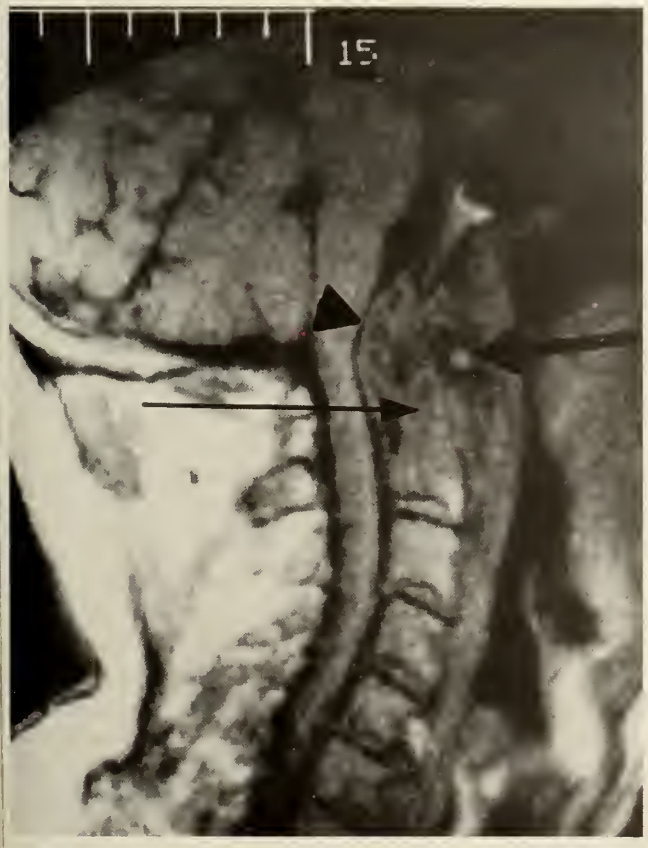

Figure 1.—A T1-weighted magnetic resonance image of the upper cervical spine shows scattered areas of decreased signal intensity in the odontoid **(thin arrow)**, consistent with acute osteomyelitis. A prevertebral soft tissue mass **(wide arrow)** extends down to the fifth cervical vertebra; an epidural mass **(arrowhead)** compresses the upper cervical cord and medulla.

Figure 2.—A T1-weighted image after the intravenous administration of gadolinium shows enhancement of the prevertebral **(wide arrow)** and epidural **(thin arrow)** soft tissue masses. Spotty areas of enhancement are also present in the odontoid.

not done. Because of the polymicrobial flora identified and the possibility that obligate anaerobes may also have been present, the patient was treated with a regimen of imipenem, an agent with broad activity against such mixed flora. The drug was given intravenously in a dosage of 500 mg every six hours. Quantitative susceptibility studies confirmed that each of the bacterial species was highly sensitive to imipenem (Table 1).

The patient had an uneventful postoperative course. He became afebrile within 24 hours, his neck pain gradually decreased, and he regained full range of motion of his neck in about four weeks. He continued to receive imipenem intravenously for three months. Follow-up MRI examinations showed T1-weighted images with increasing signal intensity in the odontoid bone marrow; these changes were thought to be compatible with healing osteomyelitis.

Discussion

The difficulties encountered in recognizing the presence of lumbar, thoracic, and, especially, cervical spine osteomyelitis are well known.[9] Infection of the vertebral body may arise as a result of direct extension from a contiguously infected site[2,4] or by hematogenous dissemination from a remote focus of infection.[1,3,5] We can only speculate about the pathogenesis of our patient's cervical osteomyelitis. Culture of blood specimens showed no growth, and he had no discernible distant infection that could have seeded the odontoid bone. He had a three-week history of sore throat, however, and presented with a retropharyngeal abscess yielding bacte-

TABLE 1.—*Minimum Inhibitory (MIC) and Bactericidal (MBC) Concentrations of Imipenem for the Bacterial Species*

Concentrations, μg/ml	Staphylococcus aureus	Lactobacillus casei	Lactobacillus fermentum
MIC	0.5	0.39	≤0.05
MBC	0.5	0.78	≤0.05

rial species indigenous to the mouth. It is plausible that his odontoid osteomyelitis arose secondarily from this adjacent and possibly primary oropharyngeal infection.

In contrast to classic descriptions of the clinical acuity of retropharyngeal abscess,[10] our patient's condition on presentation was notably subtle and indolent. Nonetheless, the early use of MRI in his case demonstrated clearly the extent of involvement of the odontoid process and surrounding tissues and led appropriately to emergent surgical intervention. Furthermore, serial magnetic resonance imaging during and after his antibiotic therapy trial provided an objective assessment of the rate of healing of the odontoid lesion.

This case shows that cervical osteomyelitis may occur in the absence of identifiable, predisposing underlying disorders and that imaging of the neck and pharyngeal space with MRI technology can facilitate the recognition of what might otherwise be a covert, yet highly destructive, infection in the upper cervical spine.

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Commentary

The 'No Code' Tattoo—An Ethical Dilemma

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Out-of-hospital death in the United States has become a ritual punctuated by sirens, cardiopulmonary resuscitation, and advanced cardiac life support (ACLS). Emergency physicians are increasingly concerned with the misuse of ACLS, including the practice of continuing it in emergency departments in most patients who do not respond to prehospital attempts at resuscitation.[1-5] Patients are equally concerned. Individual patients do not know how to ensure that their wishes concerning resuscitation will be carried out. These uncertainties have been intensified by the US Supreme Court's decision in *Cruzan versus Missouri Department of Health* allowing states to require "clear and convincing" evidence to withdraw life support.[6] In this commentary I describe one person's attempt to control the circumstances of his own death.[7]

No Code Tattoo

On his 65th birthday, a physician with more than 40 years of clinical experience in emergency medicine and general (trauma) surgery who was board certified in both, had a tattoo symbolizing "Do not defibrillate or cardiovert" (DND) placed on his left chest. This tattoo (25 mm in diameter) (Figure 1), copied from a picture prepared by a medical illustrator, was positioned lateral to his left areola. The tattooed symbol was used because it is an international form of communication not requiring words. As such, his desires would remain comprehensive if he were to die during his frequent foreign travels. Placing the tattoo represented neither an end-of-life nor an end-of-career action. The physician had neither retired nor reduced his workload and had no serious or debilitating disease. He continued to teach, work clinically, and do research on a schedule at least as full as that of his younger colleagues. He formally retired at age 70 but continued to see patients and do research for part of the time.

Several questions are raised by this action:

- Why did this experienced clinician feel it necessary to get such a tattoo?
- How adequate are current advance directives, especially in prehospital care and in emergency departments?
- How should clinicians respond to such nonstandard directives in emergency situations?

Why Did This Physician Feel It Was Necessary to Have This Directive Tattooed on His Chest?

A DND tattoo can be seen as a response to retirement, illness, or depression or, to the contrary, as an affirmation of personal principles. If it is a statement of personal principles, the underlying motivations and the nature of a medical care system that requires such action are worth investigating.

> I think ACLS is a farce (he says). Paramedics save lives by defibrillation, but we never save them in the emergency department unless the paramedics bring them through the door with a pulse. I don't mind dying, but I sure as hell do not want to spend days, months, or years in a nursing home bouncing beach balls in a parachute blanket.

This physician created his tattoo as an attempt to make a principled statement about the futility in emergency departments of continuing ACLS on patients who do not respond to prehospital resuscitative efforts. His active and productive life after acquiring the tattoo attests to his not using it as an end-of-life statement. The tattoo demonstrates his own dismal experience with continuing unsuccessful prehospital ACLS in an emergency department, an experience confirmed by other emergency physicians experienced in prehospital care.[1-5]

In contrast to several published accounts of emergency department resuscitations,[8] emergency physicians seem to be swinging toward the conclusion that nearly all patients arriving without vital signs in an emergency department either quickly die or have devastating neurologic sequelae. A recent study from Baylor College of Medicine, Houston, Texas, suggests that less than 0.01% of patients having prehospital cardiac arrest leave the hospital alive.[1] Other studies have shown similarly dismal results, concluding that between 0.4% and 0.6% of patients who undergo prehospital resuscitation leave the hospital neurologically intact.[4,5] Even in hospitalized patients, only 11% to 17% of those who have CPR done leave the hospital.[9,10] Newer terminology regarding the limitation of medical care orders implicitly recognizes these data. Once common, "do not resuscitate" (DNR) orders are now changing to "do not attempt resuscitation" (DNAR) orders.

The overuse of ACLS is a reflection of medicine's general attitude toward diseases and patients. Physicians are often more concerned with errors of omission than with those of

Figure 1.—The tattoo next to the patient's left areola (actual size, 25 mm in diameter) signifies an international code for "do not defibrillate."

(Iserson KV: The 'no code' tattoo—An ethical dilemma. West J Med 1992 Mar; 156:309-312)

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ABBREVIATIONS USED IN TEXT

ACLS = advanced cardiac life support
CPR = cardiopulmonary resuscitation
DNAR = do not attempt resuscitation
DND = do not defibrillate or cardiovert
DNR = do not resuscitate

commission.[11] One theory of error control in medical practice suggests that when an error is likely to occur, the course of action with the most preferred result (or least egregious error) is chosen. Following this reasoning, emergency physicians and the emergency medical system may be more troubled by failing to resuscitate those few people who possibly could be saved than by resuscitating the many people who cannot be saved or do not want attempts at resuscitation.[11] Even though it is generally accepted that adult competent patients can refuse medical treatment, this seems to have been ignored in cardiac resuscitations. As George Annas said,

> Although CPR is almost 20 years old, the general rule today often seems to be that no one can die in a hospital without CPR. This is medical practice in many institutions, *but it is not the law.* Patients have the legal right to refuse to be resuscitated [emphasis in original].[12(p216)]

The physician who had himself tattooed attempted to prevent resuscitation efforts that would only prolong his dying and impose unnecessary suffering before death occurred.[13-15] The purpose of his tattoo was to demonstrate his belief that ACLS is overused; it was not a reaction to life events. He acted in response to the modern technomedical death that as Philippe Aries says,

> has been dissected, cut to bits by a series of little steps, which finally makes it impossible to know which step was the real death. . . . the doctor and the hospital team . . . are the masters of death—of the moment as well as the circumstances of death. . . .[7(pp88-89)]

The results of this biotechnologic imperative have made traveling the road to death more laborious, painful, and costly. The tattooed physician is not the only emergency health care professional to feel the need to declare his position in favor of limiting resuscitation. Although there is no record of the frequency of DNAR tattoos, I know of one other example: an experienced and practicing emergency department nurse with "DNR" tattooed in the precordial area.

What Does a DND Tattoo Say About the Adequacy of Current Advance Directives, Especially in Prehospital Care?

One method used to guide the application of modern health care technology in accord with a patient's personal values is the signing of advance directives such as living wills, durable powers of attorney for health care, and DNAR orders. The rationale for the use of advance directives is a respect for patient autonomy, which asserts that patients should determine their own resuscitation status.[16] In the recent US Supreme Court decision in *Cruzan*, five justices declared that a constitutional liberty interest guarantees adults with medical decision-making capacity control over what happens to their own bodies.[6]

Advance directives are now commonly used within health care institutions but are less used elsewhere. In the past decade a consensus has been established that DNAR orders, a form of instructive directive, are ethically acceptable.[16] New federal law requires instruction as to the availability of advance directives for all patients in hospitals, hospices, nursing homes, and receiving home health care.[17] Even with such instruments, it remains difficult to control the circumstances surrounding one's own death outside of a health care institution.[18-20] If the emergency medical system is inadvertently activated at the time of death, prehospital resuscitation attempts are required almost everywhere in the US. Only about 23 of the many hundreds of emergency medical system jurisdictions and only two states by statutes—Montana and New York—currently have a comprehensive DNAR protocol that controls erroneously activated ambulance services and allows those dying at home, in a public place, or even in a long-term-care facility to avoid otherwise mandatory ACLS when it is neither desired nor appropriate.[20] Even where such prehospital DNAR protocols do exist, patient identification and an immediate awareness of the existence of a directive are problems this physician's tattoo reduces.[19] When patients reach the emergency department, the mandate for preserving life and the often overriding principle of beneficence limit the ability of patients to exercise autonomous decisions about resuscitation, especially through advance directives. Thus, although advance directives are becoming easier to obtain and to implement, and although federal legislation is making their use more prevalent, emergency medical system protocols that allow the implementation of DNAR in the prehospital setting are rare.

How Should Clinicians Respond to Such Nonstandard Directives in Emergency Situations?

Physicians have three options when confronted by patient directives, including a tattoo: they can follow them, ignore them, or use them merely as another piece of information to guide treatment.

Following a directive. Although there are many ways for patients to transmit information to physicians, even when they are unconscious, there are at least three requirements for every directive if it is to be implemented: it must be a true and uncoerced expression of the patient's wishes; it must be unambiguous; and the patient's directions must be morally and legally appropriate, not compromising the medical care giver.

It is often difficult for emergency care personnel, whether in the emergency medical system or the emergency department, to determine the identity let alone the wishes of their patients. They often must rely on third parties for this information. Extralegal surrogate decision making (where the surrogate is not statutorily appointed, not an agent under a durable power of attorney for health care, a legal guardian, and not the parent of a patient younger than 18 years) is fraught with problems and is best avoided in hectic emergency scenarios where life and death are at issue. In the case of the physician with the DND tattoo, however, no surrogate is necessary.

What is not clear is what the tattooed patient intended to have done (or not done) because of the tattoo. The tattoo symbolizes "do not defibrillate." Prehospital defibrillation is the one frequently lifesaving therapy in out-of-hospital cardiac arrests; 10% to 30% of patients found in ventricular fibrillation survive if defibrillation occurs within ten minutes of cardiac arrest.[21] The physician with the tattoo directive in fact said that he did *not* specifically want to forgo the possible benefits of prehospital defibrillation. He was caught in a dilemma, however, because he wanted an easily and interna-

tionally recognizable symbol indicating his wish not to undergo futile resuscitation attempts. His hope was that the tattoo would help dissuade an emergency department staff from continuing ACLS if he presented without vital signs. A "DNR" tattoo might be less ambiguous than the paddle (DND) tattoo, but a DNR tattoo also requires interpretation. Does DNR mean not to defibrillate, not to assist ventilation, not to administer intravenous fluids, or even not to administer a narcotic antagonist should it become necessary?

The ambiguity of many advance directives, both within medical facilities and in prehospital care, has led to more specificity in the directives.[22,23] Orders about whether to defibrillate, intubate, use vasopressors, operate, or hydrate are now often explicitly stated in hospital DNAR orders. This level of specificity, as well as its multitude of different legal and quasilegal formats, does not work in emergency care. Unlike the relationship between clinicians and their hospitalized patients, emergency personnel are initially unfamiliar with their patients, have limited time to effect many critical medical interventions, and may be unable to decipher nonstandard legal documents in the time available. If emergency care givers are to comply with a patient's advance directive, the directive must have a format that is standard, familiar, unambiguous, and that protects those who comply with its requests.[19] A partial solution to this problem is for more emergency medical jurisdictions to adopt prehospital DNAR protocols through which to set boundaries for prehospital resuscitation that are clear and acceptable to both patients and care givers.

If emergency care givers are to comply with a patient's advance directive, the directive itself must request moral actions, must be legal, and must not compromise the integrity of the medical profession. Advance directives carry no more weight than a competent patient's choice. Even a competent patient's ability to exercise choice about care is not absolute; societal values, expressed as state interests, can sometimes override the patient's autonomous wishes. Accordingly, advance directives may be overridden if state interests are more important.[16] These interests include the prevention of homicide and suicide, the preservation of life, protection of the interests of innocent third parties, and the maintenance of the medical profession's integrity (as enumerated in *Superintendent of Belchertown State School versus Saikewicz).*[24]

There is also a unique quality of emergency medical care that cannot be compromised: the willingness to respond to requests for help whenever asked. The emergency medical system has a duty to respond appropriately to those appearing in need of its help, without triaging on the basis of quality of life, socioeconomic status, or any other nonrelevant factor. In the absence of a prehospital directive specifying a patient's considered wishes under a standard DNAR protocol, emergency care professionals should give primary weight to the patient's immediate objective interests in avoiding significant harm and death.[25] This is the basis of all emergency medical care: if it is to be altered in response to patients' wishes, an explicit and public protocol to that effect must exist.

Ignoring the directive. Many emergency physicians are uncertain whether they may act on the basis of an advance directive in the emergency departments, especially once ACLS is in progress. This hesitancy may stem from their role as emergency care givers, from the concerns expressed earlier about the directives themselves, or from a questioning of the difference between withholding and withdrawing care. Although these factors will not cause emergency physicians to halt emergency department resuscitations, they may cause emergency department personnel to use only medical indications, not patient directives, to determine when to cease resuscitative efforts.

Although the physician's tattoo is an extreme and somewhat ambiguous format to express personal wishes, alternative methods are available and are commonly used to relay specific medical information. Patients carry Medic Alert* necklaces and bracelets, a wide variety of wallet cards, and occasionally medical records or actual advance directives to alert health care providers to their medical illnesses, hazards, or wishes. These devices most often advise medical care professionals that the patient suffers from a particular disease or allergy that may affect diagnosis and treatment. These various warnings and explanations are advisory only; they do not constitute a consent or refusal of a specific therapy.

Emergency care givers are more frequently seeing patients who, through relatives, their primary care provider, or their medical record, direct that specific treatment be withheld. Such refusals may conflict with the care givers' concepts of the principle of beneficence. Although these patients may be in the terminal stages of a progressive disease, they may also be patients with reversible conditions of abrupt onset.[26(p154)] In emergency care, with its limitations of time, patient information, and resources, the principle of beneficence weighs so heavily on providers that when a dilemma arises between whether to respect patient autonomy or provide beneficent care, beneficence controls. The bias toward attempting to preserve life is strongest in the emergency department. Emergency care givers may come to accept advance direction for terminal patients more easily, but it is unlikely that they will ever withhold lifesaving care from patients with acute illness or injury who could obviously receive a sustained and substantial benefit from treatment, even if an advance directive were known to exist.

Problems with advance directives are not limited to refusals to accept treatment; directives may also demand inappropriate treatment. Another complication may arise with the use of advance directives in the future, when they may direct physicians to continue "heroic" efforts, even when the physicians think that further treatment is futile. The Illinois durable power of attorney for health care legislation includes a proviso through which a patient may request all forms of life-maintenance treatment to be continued indefinitely.[27] If emergency medical professionals look first to the medical indications for resuscitation and rely heavily on beneficence (and its obverse, nonmaleficence) in their decision making, these demanding directives will probably have less force than other advance directives because patients have stronger legal and moral rights for refusing than for demanding therapy.

Use as information. Some emergency physicians may use standard advance directives as well as nonstandard directives including a tattoo as merely another piece of information to be used in making medical care decisions. The more ambiguous the directive, the less probative the information. Yet, when used in the context of specific medical indications for resuscitation or continued resuscitation, the patient's preferences in the matter may be important. Even with only a tattoo indicating that resuscitation is refused, a patient may influ-

*Medic Alert, 1000 N Palm, Turlock, CA 95380.

ence the circumstances of his death as strongly as if a formal advance directive were in effect and known to the emergency care givers. With a tattoo, at least a patient can be assured that whatever the circumstances, the tattoo will be in evidence to give some weight to his or her desires concerning resuscitation.

Conclusion

In general, because of its ambiguity and the potential for compromising the integrity of both the emergency medical system and the physicians involved, neither a tattoo nor similar nonstandard directives should be followed. Physicians should, however, weigh nonstandard directives in direct proportion to their reliability and with consideration of the surrounding medical situation.

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Letter to My Future Doctor

FAITH FITZGERALD, MD, *Sacramento, California*

Everyone is talking. Physicians, politicians, newspaper columnists, patients, families, authors, talk show hosts, all are debating our right to decide how and when we will die. It is necessary and wise to obtain a medical directive. One question we must ask ourselves as physicians is, Can we *do what we ask our* patients *to do? Here is one physician's medical directive.*

We are in an era of ethical conundrums, especially in the distinction between what we *can* do and what we *ought* to do regarding the continuation of life. I admit that, knowing as much as I do, I fear your enthusiasms and your doubts. Because I do not know you yet, I want to take this chance to make myself clear to you.

I believe that my body is a vehicle for my brain, no more than a machine that allows my mind to function. So long as my brain works, that is, receives and sends coherent messages, I would wish to live.

If my brain fails—by trauma, a residual of metabolic disarray, degenerative process, tumor, ischemia, infection, or other chronic or acute event—let me die.

If I am in a chronic vegetative state, irreversible coma, or dementia to the point where I require help in basic functions—let me die.

It can be argued that you won't be sure of the permanence of such a state of cerebral dysfunction, but I don't require absolutes.

If in your best opinion the strong likelihood is for continued brain dysfunction—let me die.

I cannot make decisions now about dismemberment, physical limitations, chronic pain, "terminal" disease, and the like, since the circumstances of these may vary greatly. I would want to make a decision at the time, after talking with you.

If I am incapable and unlikely, because of the nature of my illness, ever to be capable of making such a decision, I will be by definition in the category of projected cerebral dysfunction already discussed—let me die.

What do I mean by "Let me die"? I mean let me die without vacillation: no antibiotics, fluids, enteral or parenteral sustenance, electrolyte manipulations, supportive machinery, or emergency interventions other than are necessary to relieve pain. Don't let your fear of the law, or the strident desires of others, override your common sense. Should someone accuse you of "playing God," tell them that I said that death is a natural end; it is the futile prolongation of severely damaged life that is "playing God." Moreover, I now also give you permission to take organs from me that might benefit others—eyes, kidneys, heart, skin, liver . . . whatever.

I was not for millions of years, the time before my birth; I will not be for all of subsequent time beyond my death; the one is no different to me from the other. Neither terrifies. I will die. Let it be when the mind I have defined as myself has ceased to allow me to function as a sentient being, interacting with others in a creative and independent way.

I'll make a bargain with you: I will, by this declaration, release you from your doubts about what to do, and you, in turn, will allow me to escape from a future threatened by senseless animation. Let this be our final act as colleagues.

FAITH FITZGERALD, MD
Sacramento, California

Have you written your own declarations of intent and have you notified your own physician or family about them? We challenge you, the readers of THE WESTERN JOURNAL OF MEDICINE, *to send us your comments. A public declaration will reveal varieties of opinion. It will put in writing your easy-to-say claims; it will give you an idea of the challenges involved in constructing these directives. This should be interesting!*

THE EDITORS

(Fitzgerald F: Letter to my future doctor. West J Med 1992 Mar; 156:313)

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Commentary

Ruminations of a Teaching Surgeon

ROBERT A. CHASE, MD, *Stanford, California*

I am highly honored and deeply grateful to be the recipient of this singular honor from the California Medical Association.* I would like to take a rather lighthearted approach to reviewing my world of medical education.

Laroff's credo says:

"It is not so important to be serious as it is to be serious about what's important."

One of the strong memories in my career was coming to California and Stanford University in 1963 as Chairman of the Department of Surgery. My vision over the years had been that except for the captain of an ocean-going liner, the last reigning monarch was the Chairman of a Department of Surgery. "Power, power at last," I thought to myself. So as an early initiative, I phoned the emergency department, the intensive care unit, the recovery room, and various areas to check on their facilities and readiness. I called the operating room and got the doctors' dressing room orderly. "Doctors' dressing room," said he. I said, "I would like to inquire about locker facilities for surgeons." "Well," he responded, "we have some open half singles for students and residents, some slightly rusty back lockers for attendings and visitors, and for the fat-assed professors, we have some new combination, secured, full length lockers." "Do you know who this is?" I questioned. "Nope," was his response. "This is Professor Chase, new Chairman of the Department of Surgery," said I authoritatively. "Do you know who this is?" he inquired. "Well, no," I answered. "Well, goodbye, fat ass," he retorted as the phone clicked off.

Memories

I would like to go back 47 years to 1943 when I started in the study of medicine. It was, in Dickens's words, ". . . the best of times and the worst of times," before ball point pens, pantyhose, and credit cards. Before hair dryers, second opinions, and touch-tone telephones. We didn't dare say condom out loud but had no fear of referring to hearts as young and gay. It was an age when Madonna was a statue at the local Catholic church, third-party carriers helped with your luggage, and marketing was something you did with a basket.

It was an era when TLC didn't mean thin layer chromatography and HMO was Haley's famous laxative. MR meant mister and medically indigent adults were not MIAs. MIA had the jarring and depressing meaning that it had again during the Gulf war. APCs were not armored personnel carriers. In those days physicians knew who Osler and Halsted were and fear of malpractice was not a driving force in medical decisions. Podiatrists did podiatry, general surgeons were general, and the only treatment in gastroenterology was some variation of the Sippy diet, whereas today's fiberoptic endoscopy presents endless opportunities to look into oneself. Less than a radical mastectomy would have been malpractice—if there had been malpractice. A hand-held calculator was a slide rule and AIDS identified people who helped nurses or wore pink frocks. Closets were not for coming out of. Gallbladders were removed by incision and dissection.

It was before "thank you" was said by flashing lights at the toll booth and when "have a nice day" meant have a nice day. Affirmative action was a vote at the town meeting.

It was before MRI, RVS, CME, and PPO. Oncology wasn't even a word.

We surgeons didn't know we were in a noncognitive specialty. There were no lasers, surgical staples, vascular grafts, or joint prostheses. Digital subtraction meant finger amputation, lithotripsy was a technique for jumping rope, and ultrasound came from jukeboxes.

A hospital day cost $65, and an appendectomy brought $125 maximum. Free care was freely given and Robin Hood ordered the behavior of administrators. Now it's rob the rich and pay the lawyers. It now costs more to go to the hospital than it did then to go to medical school. We didn't call firing people down-sizing or being de-selected, outplaced, or non-positively terminated, and a set of objectives was not a paradigm. Quality assurance was the wear guarantee that came with interwoven socks.

I would have thought a suppressor oncogene was an auto part or a radio tube. There were no contact lenses, throw-away syringes, cyclosporins, monoclonal antibodies, or re-certifications. A chromosomal short arm could have been misinterpreted by us Army docs.

Come and gone in my years have been—Wangensteen's gastric freezing, Smithwick's total sympathectomy, Gillies' tubed pedical flap, and a whole host of procedures now dealt with medically or radiologically.

In our days kids played doctor—now they play specialist and their little doctors' kits come with a malpractice insurance policy. In the ER they used to take your vital signs—now they take your Blue Cross number.

We were grossly deficient in what we could do physically for our patients—no open heart surgery, no endoscopic surgery, no microsurgery, no transplant surgery, but medical care meant caring for the patient. In many ways—the best of times.

What has continued as best for me is the privilege of teaching. There is real pleasure in watching and helping students develop from freshmen who think the cesarean section is a district in Rome to seniors who understand the details of genetic recombinant DNA therapy far better than I.

*Dr Chase received the 1991 Golden Apple Award, presented by the California Medical Association to recognize exceptional physicians who have made a lifelong commitment to teaching.

(Chase RA: Ruminations of a teaching surgeon. West J Med 1992 Mar; 156:314-315)

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It has been fun to observe the cyclic changes in medical school related to

- Grading versus pass/fail
- Core curriculum versus electives
- Honors versus no honors
- The early introduction to clinical medicine
- Organ systems approaches
- Problem-oriented learning
- Thesis requirements
- Attitudes towards the National Board Examinations

There are lots of experimental curricula as at Case Western Reserve, McMaster University, Miami, and Harvard with their "New Pathway." Our generation can be characterized as one offering French in kindergarten and remedial English in college. In academic medicine we see evidence of this when reading histories. Here are some entertaining chart entries:

This gentleman urinates around the clock every four hours.

A 54-year-old woman arrived with abdominal distress—she has constipation on the one hand and diarrhea on the other.

This 30-year-old male is married—no other serious illness.

Or a prescription I saw that read, "Tenactin suppositories, dispense 24 (such) Sig: Insert one every four hours until exhausted."

What incredible satisfaction I have had in watching the unfolding of the careers of students and trainees. Recommending them for the next step in their careers is generally one of the pleasures. Yet, in today's era of freedom of information, letters are available to the student or trainee. This has led to what Lederer calls the "mangled modifier" strategy for letters of recommendation. Watch for varying interpretations in letters describing students. For example:

For the lazy student

"You'll be lucky to get Harvey to work for you," or

"I can't recommend him too highly."

For the person in trouble with the law

"He is a man with many convictions."

For the heavy drinker

"I spent many happy hours with Hubert."

Participating as a CME instructor is always profitable educationally, since one learns from the participants. Although ours has been identified as a learned profession, its proudest attribute is that it is a *learning* profession.

As a teacher, do I have concerns? Of course I do. I have noted with some alarm the drop in the number of applications to medical school—about 31% over the last decade with an applicant-to-billet ratio going from 3.5 applications to one position in 1950 to 1.6 to one in 1990. Fortunately, this year's application numbers have started to rise. Disturbing, however, were data from the American Association of Medical Colleges survey of students who took the MCAT, then did not apply to medical school. Of these, a half had chosen alternative careers, and 30% of these were advised against medicine by physicians predominantly from the older generation.

I am concerned at the growing average indebtedness of our graduates. In 1989 the average debt for medical school graduates was $42,374—nearly twice what it was in 1987.

I worry that medical schools have become more dependent upon faculty-earned practice funds. In 1971 practice funds furnished 12% of total school revenues, whereas in 1990, 43% of revenues came from faculty practice earnings.

The Future

In the years ahead, our profession generally has enormous new problems to solve. A simple listing of a few of the issues might include

- The continuing struggle to meet the health care needs of our citizens versus the reality of budget constraints and deficit reduction
- Over 30% of babies admitted to inner-city intensive care units are born to "crack" abusing mothers, and 2% or 3% are positive for the human immunodeficiency virus (HIV)
- An estimated 1 million people in the United States are HIV-positive
- 37 health care workers are thought to have contracted HIV infections on the job, largely from needle sticks
- 14% of medical schools report medical students or residents who are HIV-positive
- 40 surgeons and 144 dentists are known to have the acquired immunodeficiency syndrome, and the Centers for Disease Control estimates at least ten times this many are HIV-positive
- Old diseases such as measles are reappearing—13,000 cases in the United States in 1989
- The whole issue of positive euthanasia
- The problem of physician participation in executions for capital punishment
- Sex between physicians and patients, said to have an incidence of 5% to 10% among psychiatrists
- The need for guidelines on ethics of various drug house gifts and favors
- The growing evidence of fraudulent research

And the list goes on.

Above all, we must not let problems, challenges, and advances cloud those wonderful attributes of our profession and its activities that are changeless. Quantitatively, most clinical medicine is straightforward. It is our privilege to help most patients because they have simple curable disorders, and it is equally important that we offer effective reassurance to the one-third to one-half of patients coming to us who have no physical or biomedical ailment. In academia we are inclined to search for zebras.

Responsibility at a distance as in "managed care" will never substitute for a physician's responsibility for his or her patient. I find that the apparent ease with which a problem may be solved is directly proportional to one's distance from the problem. Since a physician knows more than anyone else about his or her patient, he or she is, by definition, captain of the health care team.

Next to being shot at and missed, nothing is really as satisfactory professionally as a good surgical outcome recognized by both the patient and the surgeon. A poor result makes one wish that the shot had not missed.

Despite the fact that we may all become salaried employees with rules based on cost, faced with ethical issues of monumental proportions because of emerging technologies, and despite the specter of malpractice litigation and diminishing public respect, as well as demands of society through third-party carriers and government, despite all of these, the most precious gift of all—the relationship between physician and patient—remains and always will remain in our hands.

Editorials

Kindliness Is Next to Godliness

NOT LONG AGO I was a member of an audience listening to a presentation on medical ethics, death, and dying. The message was to assure good, fair decisions. The speaker espoused "death with dignity." An older physician in front of me leaned toward a long-time colleague and muttered, "There's no such thing as death with dignity." I snapped to full attention. Surely death is not always a struggle. But many people, comfortable with having made plans for dispersing their goods and having said I love you and I forgive you and I cherish and respect you to important people in their lives, welcome the idea of dying in their sleep—on their own schedule. No one wants to linger; no one wants to linger in the disoriented way reported in one of the *Lessons From the Practice* appearing in this issue.[1] But wishes may not come true; fate may not honor preferences. How can physicians work toward assuring a patient's death with dignity, "dying in character," as Elisabeth Kübler-Ross calls it?[2]

Several forces act distinctly against death with dignity. Although the use of technology presents great opportunities, it has unmistakable drawbacks. It can reverse downhill trends. It can foster a return to normal. It can make marvels. But it can also be unnecessary, uncomfortable, downright painful. It can prolong life, and death. Its beneficence can be countered by side effects and inappropriate use. The same is true for our impressive pharmacopeia. In addition, the fast pace of life and the ever-growing size and complexity of the health care system compound the impersonal brush-off that many patients feel as they are tossed in a churning current, seeking care. They long, as do we, for a still time, a healing time, a time when we can put into effect the implications of the Asian aphorism: We are given two ears and one mouth.

Even during these turbulent times, there are beacons and anchors, principles to guide us. As we study, discuss, and debate biomedical ethics, we absorb concepts about patients' autonomy, about giving them choices and about respecting their choices. We also acknowledge the need for care that is whole and equitable and not based on the ability to pay or on social class. We are reminded that *primum non nocere* is a powerful directive, probably even more powerful than preventing harm and doing the right thing. Of course, we can assure the thoughtful use of technology and pharmacology. We can resist other forces that act against death with dignity by being sensitive to the oft-unspoken needs of patients. We can also add another litmus test to our armamentarium. This test may be the most important of all, yet it seems neglected in canons and weighty discourses. It is pure. It is personal. It is quiet. It is the test of kindness.

Poets and playwrights, authors and philosophers have noted through the centuries that kindness brings warmth to the giver and the receiver. William Wordsworth valued "that best portion of a good man's life, his little, nameless, unremembered acts of kindness and of love."[3] Robert Burns, a few years earlier, lauded "The heart benevolent and kind . . . most resembles God."[4]

Along with our capabilities, we need to develop our sensibilities. The challenge is to temper the wind to the shorn lamb. We have many strong "winds"—of machines and medications, of haste and distraction. We have many vulnerable patients. Fortunately, we have ways to light our path, to lighten our path, to assure death with dignity. One is, be kind.

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The Medical Waste Stream

THE QUESTION OF WHERE and how to get rid of our solid waste is one of the latest issues to affect heavily populated areas of the United States. There are many background stories that have made headlines throughout the country and raised the issue as a major item on the political agenda. In the summer of 1987 a barge loaded with garbage from Long Island, New York, was refused entry at various ports of the United States and Latin America. The barge eventually went to New York City, where after considerable political wrangling its load was accepted for incineration. In 1987 and 1988 newspapers were filled with stories of medical waste washing up on beaches of various states along the coast. This adversely affected the beach areas' tourist trade.

The movement to increase the regulations governing the disposal of medical and solid waste has been further accentuated by environmental concerns, such as the closure of many landfills, the dwindling capacity of others, the interstate shipment of garbage, and the difficulty of finding new sites for waste disposal facilities. Vociferous local opposition groups frequently prevented the establishment of new landfills or incinerators in their communities.[1]

In addition, some waste haulers have been charged with having organized crime connections or with restraint of trade through noncompetitive agreements. Some states have initiated licensing programs for waste haulers that require a police background check, comprehensive regulation of business practices, a policy of directing where and how the hauler will carry the solid waste, and a disposal fee and other taxes to fund an effective regulatory enforcement program.

The cost inflation, the decreasing availability of alternate disposal sites, growing local opposition to changing solid waste management practices, health concerns about alternate disposal methods such as incineration, and fears about hazards perceived to be associated with medical wastes have increased political involvement. This has led to new laws and regulations that are designed to implement a cradle-to-grave regulated waste management program. Health and political concerns may result in especially stringent regulations to control medical waste.[2]

Federal regulations became effective on June 22, 1989, pursuant to the federal Medical Waste Tracking Act of 1988. The law directs the US Environmental Protection Agency (EPA) to establish a 2-year demonstration program for tracking medical wastes. The states of Connecticut, New Jersey, New York, and Rhode Island and the Commonwealth of Puerto Rico are participating in the program.[3] The regulations list the medical wastes to be tracked and designate standards for separating, packaging, and labeling medical

wastes before sending them for treatment or disposal. The law also mandates a system of registration, recording, and fee payment for all generators. Institutions that generate more than 50 pounds of medical waste per month, such as hospitals, are subject to different regulations from those producing less waste, such as physicians. The demonstration program was completed on June 22, 1991, and the EPA evaluation will help determine whether such a program should be extended nationwide.

It should be stressed that the demonstration program currently involves only regulated medical wastes generated in one of the states participating in the program. The federal law defines medical waste as ". . . any solid waste which is generated in the diagnosis, treatment, or immunization of human beings or animals, in research pertaining thereto, or in the production or testing of biologicals . . . ."

In the decade 1979 to 1988 for the largest city in New Jersey, Newark, the amount of waste generated increased about 20% while the population serviced declined. In contrast, the cost of disposal increased more than 1,000%, and the rate of increase has been escalating in the last few years.[4] This runaway cost inflation has occurred despite municipal development of management plans that included "maximum practicable use of resource recovery (recycling) and energy recovery." This inflationary trend is further aggravated by the fact that five states hold 34% of the nation's existing landfills (Reason Foundation, Los Angeles, Calif). The cost inflation has been especially severe in the northeastern section of the United States.[5]

While the standards and cost inflation have varied from state to state depending on local factors that affect disposal costs, the additional expenses and extra work associated with the disposal have affected all health care institutions and providers. While disposal costs have been increasing at a hyperinflationary rate, political, regulatory, and planning processes are being implemented to control the overall cost of medical services.

An article in the *New England Journal of Medicine* stressed the need for the US medical care industry to reduce administrative costs to the levels seen in Canada. Dr Steffie Woolhandler estimated that administrative costs consume about 24% of total health care spending in the United States, or about $175 billion annually. In contrast, Canada spends only about 11% of its health care budget on administration.[6,7] Waste disposal is a small but increasingly important administrative overhead cost. Physicians and medical care administrators must provide increased scrutiny to control these costs.

Issues such as natural resources, the constant increase in the use of disposables, the newer nonrecyclable materials used in medical practice, and the entire spectrum of environmental political issues are having an effect on the medical care community. Medical care providers are beginning to realize that something must be done to reduce the volume of hospital and medical waste. We need to be better informed and more concerned about environmental effects associated with medical practice. Only recently have health care professionals begun thinking about the possibilities of using substitute products, of recycling, or of minimizing the use of disposable products. Gilden and colleagues, elsewhere in this issue, have suggested some means of reducing nonhazardous hospital waste and have recommended alternatives that save resources, reduce disposal costs, and conserve limited landfill space.[8]

The substitution of cloth for disposable diapers is one of the many proposed alternatives to reduce the waste stream. Manufacturers have tried to counter this with claims that their diapers biodegrade in a few years when disposed of in a landfill. The Federal Trade Commission on August 29, 1991, announced the signing of a consent agreement with a California company to cease advertising that its disposable diapers will break down in three to five years after placement in a sanitary landfill. This is the first case by the federal government involving claims that a product is biodegradable. Lee Peeler of the commission's advertising practices division stated it is "one of what we expect to be a series of FTC cases in the environmental claims area" ("California Diaper-Maker Will Dispose of Environmental Claim," *Newark Star Ledger,* August 30, 1991). Health care professionals should plan based on cost and waste reduction factors as their predominant concerns. A manufacturer's claim is not necessarily based on fact.

What we fail to do voluntarily and by example may be decided for us. Congress is expected to consider legal mandates requiring states to achieve specific recycling levels and to "beef up" government procurement preferences for products containing recyclable materials. There is also talk of a front-end national disposal tax (R. Scarlett, vice president, Reason Foundation, Los Angeles, California).

The US health care industry is behind that of many other nations in learning how to manage our solid waste. A 1987 study by Inform, a research firm headquartered in New York City, revealed that Japan uses a three-pronged approach to its successful waste management system. Japan recycles more than 50% of its wastes, compared to just 8% in the United States. In Japan, each category of waste has an appropriate place, both in terms of environmental protection and in keeping waste management costs down; in the year of the study, 50% of all paper and 66% of all bottles were recycled. By comparison, the report stated the United States recycled only about 25% of its paper and 7% of its glass (G. Bishop, "Japanese Approach to Garbage Disposal Provides a Model for Jersey," *Newark Star Ledger,* November 12, 1987, p 33). Inform's study attributes part of Japan's success in managing solid waste to its "extraordinarily precise data on municipal solid waste generation, recycling, materials recovery, incineration, and landfilling" (Inform, "Japan Knows How to Handle Solid Waste," *Bridgewater Courier News,* December 14, 1987). The resource accounting system helps allocate capital, labor, and other expenses efficiently. We have made considerable progress since this report was published in 1987, but we have a long way to go.

The medical care industry should take the lead in developing a system to reduce the quantity, environmental effects, and costs of our medical waste stream. It is important that physicians and medical care institutions develop waste management programs to more effectively control all wastes, including infectious, hazardous, and ordinary solid waste. Medical professionals must consider a new factor affecting how they function: environmental effects.

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Rational Approaches to Breaching the Blood-Brain Barrier

SINCE PAUL EHRLICH'S remarkable observation that injecting dye into the vasculature of mice deeply stained virtually all tissues while the brain remained pearly white, neuroscientists have been intrigued by the cellular mechanisms that mediate the selective transport of most nonlipophilic compounds into the brain parenchyma. The UCLA Interdepartmental Conference reported in this month's journal[1] identifies two important strategies that are currently being pursued in attempts to enhance drug delivery across this blood-brain barrier and into the central nervous system. The importance of such investigations is highlighted by two important themes. It is now clear that a much broader scope of central nervous system disorders than had previously been appreciated might be amenable to treatment with drugs. Also, technologies emerging from advances in molecular genetics and nucleic acid biochemistry are providing insight into the pathogenesis of affective, degenerative, and malignant disorders, which should identify novel targets for therapy and thereby require new agents that must enter the brain parenchyma if they are to be effective.

The blood-brain barrier is a functional concept that encompasses physiologic, anatomic, and molecular dimensions. Typically, polar substances in the circulation are not taken up by brain tissue, and nonpolar substances pass into the brain in a manner that reflects their lipid solubility. The barrier is generally agreed to be located in the cerebral capillary endothelium, which is distinct from vascular endothelium found in other locations in that it is devoid of fenestrations. Also, adjacent endothelial cells are linked by continuous tight junctions, which are thought to be impermeable to the passage of all molecules. Astroglia may contribute to this barrier in that astrocytic processes are well documented to be very closely opposed to blood-brain barrier capillaries.

Biochemical opening of the blood-brain barrier has long been examined as an approach to facilitate transport across the barrier, but even aggressive attempts at osmotically opening the barrier by infusion of hyperosmotic solutions has had disappointing results to date. Indeed, few disorders other than malignancy have been recognized as warranting the pursuit of such an approach, and ironically the barrier is invariably compromised within tumor parenchyma. Drugs apparently breach the barrier in these locations, although the interface of tumor and normal tissue and tumor cells that may have migrated away from the tumor mass remains an important problem whose consequences might be mitigated by techniques to open the blood-brain barrier. As described by Dr Keith Black, the availability of biologicals, such as leukotrienes, to enhance vascular permeability in damaged central nervous system vessels associated with pathologic states such as malignancy raises the possibility of pursuing a biologically based strategy to selectively bypass the barrier. In this regard, identifying the physiologic mediators of vascular permeability in the central nervous system may give new opportunities for the design of novel pharmacologic agents to mediate transport across the blood-brain barrier. If vessels within the brain use different regulatory molecules from those important in the systemic circulation, it may be possible to regionally modify the barrier and provide a degree of specificity not previously anticipated for treatment with either antineoplastic or psychotherapeutic agents.

A key feature of the blood-brain barrier is that it selectively inhibits the transport of hydrophilic molecules into the central nervous system. Such molecules cannot passively diffuse across the membranous design of the blood-brain barrier, and in recent years specific transport mechanisms that account for the physiologic transport of nutrients and other molecules, including glucose and amino acids, have been identified and characterized. One such mechanism, transcytosis, is discussed in the UCLA Interdepartmental Conference as the basis upon which novel approaches to the delivery of drugs to the central nervous system might be developed.

Transcytosis is a specialized pathway of intracellular transport that may be shared by the blood-brain barrier and at least in part with other tissues such as epithelia. Like the barrier, many epithelial tissues consist of cells, linked by tight junctions, that must regulate the entry of molecules from the surface they line into the tissue upon which they sit. Transcytosis requires that the molecules to be transported be taken up at the cell surface, directed to the opposite cell surface, and released into the extracellular space. Clearly if hydrophilic molecules are to cross the blood-brain barrier, specific transport mechanisms consisting in some cases of carrier proteins and receptors must exist within the membranes themselves. Based upon biochemical and physiologic evidence, the existence of such transport systems has been hypothesized for a wide variety of molecules ranging in complexity from individual amino acids to complex macromolecules. As outlined by Dr Pardridge, molecules that are taken through the blood-brain barrier into the brain parenchyma by the process of transcytosis might be used as vectors to carry along therapeutically active molecules.

For molecules such as glucose and transferrin, specific transporters have been identified. Other compounds such as cationized albumin traverse via absorptive-mediated transcytosis. Little is known of the molecular details that might provide insights into the precise mechanisms by which such ubiquitously expressed transporter systems might regulate entry into the central nervous system. Nonetheless, such systems may offer effective vehicles with which to breach the barrier. We are learning about the cellular pathways that mediate the directional transfer of molecules across polarized cells. Recent studies of epithelial tissue indicate the existence of specialized vesicular carriers that mediate the directional transport of proteins across cells and the identification of molecular signals, such as protein phosphorylation, that may mediate the selection of proteins for transcytosis, rather than some more common fate such as degradation or recycling. These studies provide evidence that an understanding of such details will enhance our potential for using either these systems themselves or pharmacologically manufactured agents that mimic the components of these pathways

to effectively increase drug uptake in the central nervous system.

The promise of biotechnology, as exemplified in the studies presented in this month's UCLA Interdepartmental Conference, is that an understanding of the physiologic mechanisms by which organisms regulate biologic processes will suggest novel approaches to the development of both preventive and treatment strategies for a broad spectrum of diseases. An understanding of the mechanisms by which the blood-brain barrier physiologically transports molecules that must enter the brain for proper function and excludes those molecules that are noxious to it will greatly complement efforts to design strategies to enhance the uptake of therapeutic agents into the brain. As our knowledge of the biochemical basis for the physiologic transport of substrates across the barrier increases, new opportunities for both the design of drugs and the targets at which therapeutic intervention might be directed will emerge. Some hints of this future, as reviewed in this month's journal, are now available for view: chimeric molecules that incorporate the physiologic substrates of specific blood-brain barrier transport mechanisms as vectors may be feasible; identifying transport systems that are specifically or selectively expressed in the brain may provide a degree of targeted drug delivery not otherwise possible; and biologically active mediators of vascular permeability that may have a role in selectively enhancing the permeability of vessels affected by pathologic disorders can be identified. Beyond these one might imagine drugs specifically engineered to include the molecular signals that are likely to specify recognition by a specific transport system and even agents that specifically modify transporter systems in a manner to facilitate their effectiveness in mediating drug transfer. Each of these possibilities holds in common an origin in the physiologic basis upon which the blood-brain barrier functions and as such can be rationally approached rather than relying upon the legacy of drug discovery that historically rested largely upon trial and error spiced with serendipity.

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Utility of 'Liver Function Tests' in Alcoholic Patients

ALCOHOLISM IS widespread throughout the United States. The illness and disaster associated with ethanol abuse are costly on both a personal and societal level. Although medical complications are common and frequently encountered by all medical practitioners, alcoholism often goes undiagnosed. In order to reduce the incidence of alcohol-related medical illness, alcoholism and its complications need to be identified early. Laboratory tests may play an important role in this endeavor. Equally important, once complications of alcoholism are identified, it is imperative to be able to accurately determine their magnitude. Because ethanol affects virtually all organs in the body, as described by Magarian and colleagues in this issue,[1] a wide array of laboratory test results frequently are abnormal.

Liver involvement is probably the most common and best characterized form of organ injury encountered in the alcoholic patient. Not surprisingly, then, the most prominent laboratory test results encountered in alcoholic patients often are those that reflect disease of the liver. Therefore, liver tests serve three major functions. First, in a patient who refuses to admit ethanol abuse, they may alert the physician to the presence of alcoholic liver disease and hence alcoholism. Second, in a patient with apparent liver disease, they are useful to help differentiate alcoholic liver disease from nonalcoholic liver disease. Third, also in a patient with known liver disease, they help the clinician ascertain the degree of injury. Because optimal diagnosis and management depend on recognizing and interpreting the results of such tests, it is essential that physicians be familiar with them.

Laboratory tests are important because they provide a simple, noninvasive method for evaluating diseases. Unfortunately, no laboratory test is pathognomonic for alcoholism. Since ethanol is metabolized in the liver and has a propensity for causing damage to this organ, tests of liver injury often provide the first clues to alcohol abuse. Although biochemical tests related to the liver tend to be diffusely abnormal and may be confusing, certain patterns of change are often present and can be recognized. Commonly referred to as liver function tests (LFTs), the serum aspartate aminotransferase (AST, formerly SGOT), serum alanine aminotransferase (ALT, formerly SGPT), alkaline phosphatase, γ-glutamyl transferase (GGT), leucine aminopeptidase (LAP), 5′-nucleotidase, and bilirubin levels may demonstrate evidence of alcoholic liver disease. When evaluating patients with alcoholic liver disease (or any other liver disease), it is useful to group tests into the following general categories:

- Tests that detect injury to hepatocytes (AST, ALT);
- Those that detect cholestasis (alkaline phosphatase, LAP, 5′-nucleotidase);
- Tests of the liver's capacity to transport organic anions (bilirubin); and
- Tests of the liver's biosynthetic capability (true liver *function* tests) including the serum albumin and prothrombin time, the latter of which reflects the liver's synthesis of blood clotting factors.

The most sensitive tests for detecting ethanol-induced liver injury are the aminotransferases. These intracellular enzymes are released during hepatocyte damage or death. Relatively large amounts (>1,000 IU per liter) may be released during viral or toxic liver injury as cell membranes are disrupted, but because of the vast number of hepatocytes present in normal human liver, liver function may remain intact. Thus, aminotransferases are tests of hepatocyte integrity rather than liver function. The AST level is elevated in 43% to 100% of patients with alcoholic liver disease, although the degree of elevation does not correlate with the severity of the pathologic lesion.[2] For example, the AST level may be elevated with only fatty changes yet may be normal with advanced cirrhosis. In patients with alcoholic liver disease, the AST level is usually elevated only twofold to fivefold, regardless of the extent of hepatocellular damage. Very high (such as >10 times normal) AST levels are distinctly unusual in alcoholic liver disease, and their presence should

raise the suspicion of other causes of liver injury, particularly those in which hepatocellular injury is prominent. In contrast to AST (which is found in skeletal muscle, heart, kidney, and brain, as well as liver), ALT is found only in liver and thus is attractive as a potentially specific indicator of liver disease. Serum ALT levels, however, are frequently normal or minimally elevated in patients with alcoholic liver disease, even in those with severe histologic damage, and are therefore a poor marker for this disease. Determination of the AST:ALT ratio has been extolled as useful for confirming the diagnosis of alcoholic liver disease or differentiating it from liver disease not related to alcoholism.[3-5] The reason for the elevation of the AST level out of proportion to the ALT level appears to be a differential reduction in hepatic ALT due to deficiency of the cofactor, pyridoxine-5-phosphate.[6] Early studies indicated that an elevated AST:ALT ratio (such as > 1) suggested that alcoholic liver disease was more likely than other liver disease.[3] For example, 91% of patients with alcoholic liver disease had an AST:ALT ratio of >1.0 and 70%, a ratio above 2.0. Further, only 11% of patients with postnecrotic cirrhosis, chronic hepatitis, and viral hepatitis had an AST:ALT ratio >2.0. Later studies have tempered this initial enthusiasm. For example, in the Veterans Affairs cooperative study on alcoholic hepatitis, 93% of patients had an AST:ALT ratio of >1.0, but only 58% had a ratio of >2.0.[5] Patients with mild alcoholic hepatitis were more likely to have a ratio closer to 1.0 while those with severe alcoholic hepatitis were more likely to have a ratio above 2.0. From a practical standpoint, an AST:ALT ratio of >2.0 strongly suggests the diagnosis of alcoholic liver disease but does not preclude other diagnoses. Additionally, an AST:ALT ratio of ≤1.0 is most compatible with nonalcoholic liver disorders but may be seen with alcoholic liver disease, especially with the less severe lesions. Thus, determining both aminotransferase levels is important in patients suspected of having alcoholic liver disease, since these tests may be helpful not only in identifying these patients but also in differentiating them from those with other forms of liver disease.

Enzymes that detect cholestasis are often diffusely abnormal in alcoholic liver disease. The alkaline phosphatase, elevated in many liver disorders, is not useful for distinguishing alcoholic liver disease from other forms of liver disease. In a patient with an alkaline phosphatase measurement out of proportion to other liver tests, it is essential to document that the alkaline phosphatase is derived from the liver by confirming elevation of at least one other enzyme that denotes cholestasis. The alkaline phosphatase level is elevated in most patients with alcoholic liver disease, generally less than threefold normal. A small subset of patients with alcoholic liver disease may present with a cholestatic picture and an alkaline phosphatase level above four times normal, however.[7] These patients characteristically have notably higher bilirubin, aminotransferase, and lower albumin levels than their "noncholestatic" counterparts. Pathologically, they have not only marked cholestasis but also substantial hepatocellular injury and fibrosis. γ-Glutamyl transferase levels are usually elevated in patients with alcoholic liver disease. The mechanism of hepatic GGT elevation is different from that for alkaline phosphatase and appears to be via induction by ethanol rather than release by necrosis. For this reason, it has been proposed as a sensitive predictor of alcoholism and of alcoholic liver injury.[8] Unfortunately, it has not proved to be useful for this purpose. Leucine aminopeptidase and 5′-nucleotidase levels tend to parallel the alkaline phosphatase levels and typically are moderately elevated in most patients with alcoholic liver disease.

Serum levels of bilirubin tend to be extremely variable in patients with alcoholic liver disease but are generally elevated. As with enzymes that detect cholestasis, bilirubin levels are also elevated in a wide variety of hepatic diseases, making bilirubin an insensitive test for identification of alcoholic liver disease. Bilirubin, however, may be helpful as a prognostic indicator in these patients. For example, extremely high levels (such as >342 μmol per liter [20 mg per dl]) in patients with severe alcoholic hepatitis portend a poor prognosis.[5]

The laboratory tests that most accurately assess liver function in patients with alcoholic liver disease as well as in other liver diseases are the prothrombin time (PT) and serum albumin concentration. The clotting factors reflected in the PT and albumin are synthesized exclusively by hepatocytes and therefore reflect hepatocyte function. An elevated prothrombin time that does not correct after vitamin K administration—correction suggests nutritional deficiency—is the best indicator of impaired synthetic function and should alert the clinician to the presence of severe functional impairment. For example, an elevated PT in a known alcoholic patient with upper gastrointestinal hemorrhage greatly increases the likelihood of portal hypertension with bleeding esophageal varices. Likewise, abnormal mental status in a patient with an elevated PT raises the specter of hepatic encephalopathy. As with the serum bilirubin, the PT may be an important prognostic indicator. In patients with severe alcoholic hepatitis and a PT high enough to preclude liver biopsy, mortality is estimated at 42%.[9] The combination of PT and the serum level of bilirubin has been used to assess prognosis by a discriminant function analysis[10]:

$$\text{Discriminant function} = 4.6 \times (\text{PT} - \text{control time}) + \text{bilirubin mg per dl}$$

Patients with alcoholic hepatitis and a discriminant function above 30 generally have a poor prognosis.[5] Albumin levels tend to parallel PT levels in most patients; albumin levels of less than 30 grams per liter (3 grams per dl) suggest severe hepatic functional impairment. Several concepts are important when interpreting PT and serum levels of albumin in patients with alcoholic liver disease. First, these determinations are of no value in differentiating alcoholic liver disease from other liver disorders, and second, they are generally not sensitive predictors of early alcoholic liver disease. Also, they may be abnormal in malnourished patients without liver disease. Under the proper circumstances, however, they offer the best and most important means by which to assess liver function.

Other laboratory tests, including the level of desialylated transferrin (dTf), have shown promise for both detecting alcoholic liver disease and distinguishing it from other forms of liver disease.[4] Although the mechanism of production of dTf is unknown, it may be through the inhibition of glycosylation of glycoproteins by ethanol. The ratio of dTf to total transferrin is significantly higher (>1.3%) in patients with alcoholic liver disease than in healthy controls, patients with nonalcoholic liver disease, and those with nonalcoholic steatohepatitis.[4] This test appears to have a higher sensitivity and specificity than any of the conventional liver tests examined (AST:ALT ratio, GGT). The major drawback is that it is not widely available for clinical use.

Liver biopsy remains the "gold standard" test for diagnosing alcoholic liver disease and for judging its severity. Pathologically, ethanol-induced liver disease can be grouped under three major forms of injury:

- *Fatty liver* is characterized by replacement of the hepatocyte cytoplasm with macrovesicular fat droplets.
- *Alcoholic hepatitis* is typified by ballooning degeneration of hepatocytes, polymorphonuclear leukocyte infiltration, and the presence of Mallory's hyaline.
- *Cirrhosis* is characterized by bridging fibrosis joining portal and central zones in the liver.

Individual patients may display evidence of any one or more of these lesions. Indeed, histologic evidence of all three often is present in the same patient. Fatty liver and alcoholic hepatitis are typically reversible; cirrhosis is not. Cirrhosis often progresses to liver failure, especially in the face of continued ethanol consumption.

Histologic features of alcoholic liver disease may be seen in patients with diabetes mellitus, obesity, amiodarone toxicity, and jejunal-ileal bypass. A particularly troubling entity, nonalcoholic steatohepatitis, is encountered predominantly in obese women, and histologically resembles alcoholic liver disease. In the appropriate clinical setting, liver tests are useful in differentiating these two entities. An AST:ALT ratio of >3, a bilirubin level of 34 μmol per liter (2 mg per dl), a PT of >2 seconds, prolonged, and an elevated dTf level all suggest the diagnosis of alcoholic liver disease.[4,11]

It is difficult to precisely correlate abnormal laboratory test results with specific histologic lesions, but trends may be prominent. Careful inspection of the liver test profile often allows a rough assessment of the patient's histopathology. For example, mildly elevated aminotransferase levels alone are most compatible with fatty liver or mild alcoholic hepatitis and a good prognosis. Alternatively, the patient with hyperbilirubinemia, an elevated prothrombin time, and depressed serum albumin levels is more likely to have severe alcoholic hepatitis or cirrhosis and a poor prognosis. Thus, laboratory tests in an alcoholic patient may reflect pathologic lesions that in turn dictate ultimate outcome. An important point is that although the liver test profile is often helpful in differentiating alcoholic liver disease from nonalcoholic liver disease, up to 20% of patients with alcoholism may have histologic evidence of nonalcoholic liver disease, emphasizing the role of a liver biopsy in confusing cases.[12]

In summary, the diversity of laboratory test abnormalities encountered in alcoholic patients is remarkable. Familiarity with patterns of biochemical derangement in alcoholic liver disease will increase the likelihood of detecting this process and, thus, alcoholism. The medical history remains the best means for detecting the presence of alcoholism, however. When the history and physical examination are equivocal or misleading, laboratory tests in the alcoholic patient may be the only clues to the correct diagnosis. Moreover, in patients with known alcoholism and alcoholic liver disease, laboratory tests may yield clues to hepatic function and therefore patient management. Finally, though often useful, these tests are not infallible and cannot replace liver biopsy in patients whose diagnosis and prognosis are uncertain.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

What Do Hospitals Do With HIV-Infected Staff?

To the Editor: The debate over testing of hospital staff for antibodies to the human immunodeficiency virus (HIV) continues. Although the Centers for Disease Control has decided for the time being not to publish a list of high-risk procedures, it seems likely that decisions with regard to testing, and subsequent "management" of HIV-positive physicians and nurses, will be dealt with by local political jurisdictions or institutions.

In mid-1989, we conducted a national survey, "The HIV Testing Policies and Practices of U.S. Hospitals," which contained questions related to the presence of nonoccupationally infected staff. These telephone interviews also asked, if such persons were employed, what limitations the hospital placed upon their practice.

Of chiefs of the surgical services interviewed, 24 of 508 (4.7%), 41 of 506 chiefs of medical services (8.1%), and 60 of 558 directors of nursing services (10.8%) indicated the presence of at least one nonoccupationally infected staff member at their hospital. In total, 105 (or 18.8%) of the 558 hospitals in this sample had at least one member of their combined provider staffs who was HIV-antibody positive due to nonoccupational exposure. The presence of infected staff members was significantly higher in hospitals of urban areas of more than one million (30.1%) compared to medium-sized communities of 250,000 to one million (15.5%). Only 4.6% of hospitals in smaller communities of less than 250,000 had one or more infected staff members.

With regard to the actions taken, no hospital suspended an HIV-infected physician's staff privileges or discharged an HIV-infected nurse. In 20% to 30% of the hospitals, an infected physician's privileges were "sometimes" revoked. The major action taken with regard to nurses was restriction of patient contact to certain procedures.

While these data are 2 years old, it is clear that HIV testing of all medical and nursing staff members, particularly those of hospitals in large urban areas, will reveal the presence of persons who have been nonoccupationally infected with HIV. It is less clear how much progress has been made in the past two years in developing formal policies for dealing with these persons. Those advocating testing should be prepared to propose specific policies and procedures for dealing with the results of their testing in ways that will protect providers as well as patients, since such testing *will* reveal HIV-positive providers of care in many hospitals.

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The 'Gag' Rule—A Freedom of Speech Issue?

To the Editor: If the "gag" rule is not a freedom of speech issue, what is? When Dr Hammons says in her letter published in the December issue[1] that she does not want her "tax dollars spent in this manner," she is saying not that she doesn't wish to subsidize abortions—because it isn't the gag rule that stops that—but that she doesn't wish to subsidize information about legal options for pregnant patients. Partial information is only partial care, unless one believes that doctors or the government should make decisions for patients. Health care providers who tell only part of the truth should be required to wear warning labels such as "Caution! I may not tell you everything you need to know to make an informed decision." Then a patient can know what she's dealing with.

What would Dr Hammons think about this kind of rule being applied to her information sources? First, President Bush could decide that libraries or departments in institutions receiving federal funds cannot supply information on abortions to their staffs. Then, maybe birth control information gets "gagged." Then, who knows?

No, Dr Hammons, this *is* about freedom of speech.

BARBARA FETESOFF, MLS
San Francisco, California

REFERENCE

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How Important Is a Name?

To the Editor: "What's in a name?" wrote Shakespeare, "A rose by any other name would smell as sweet." There may—Shakespeare notwithstanding—be lots in a name. A name can carry dignity but also suggest an insult, connote degradation, or paint a dismal picture. So the rose may smell as sweet by any other name, but the loss of that name may take away some of its beauty.

The designations "physician," "nurse," "physiotherapist," and other terms applied to medical professionals not only describe their positions but, as well, their function in health care. Substituting the word "provider" takes away the substance of these well-earned titles and lumps their functions in a generic pile. In doing so, it extracts the important implications of trust, caring, and warmth.

A patient must have a close relationship with a physician, must have trust, loyalty, and confidence, all of which rolls into "my physician." The word must sit on the head of a distinct person, separated from all others. It is easy for a person to say meaningfully, "My physician was with me and saw me through the dark hours," but it does not have the same ring if we substitute "provider."

Living in an atmosphere of experimental welding of medicine and industry and buffeted by government and insurance companies, a new language is being thrust upon us to describe some old and some new relationships. This, in some

ways, erodes previously solid foundations of medicine, because words, designations, and titles carry with them well-entrenched meanings. Changing these may destroy time-honored meanings.

At the same time, this is not to play down the important contributions of the new knowledge, techniques, and nostrums that are improving by the day our outlook for sick people. But we are shortsighted if we separate these from the physician who applies them to the treatment of human illness.

It is very disturbing to be forced to replace the historically rooted "physician" with the generic "provider" offered by a new group of medical planners. The word "physician," a person skilled in the art of healing, carries with it a certain dignity. The generic word "provider," when applied to a physician, carries no such implication. The same applies to other medical professionals such as "nurse" and "physiotherapist."

At a time in our history when medicine is suffering severe criticism from many sides, we must not further take down our image. We must continue to orient ourselves toward the care of the patient and continue to see that we give the most skilled care. We must resist invasion of our profession by those who do not understand the care of the sick.

Machines, laboratories, and corporations do not heal the sick—doctors do! Call us physicians, and we will continue to accept the responsibility this title implies.

PHILIP M. ENGLUND, MD
Casa Blanca Clinic
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LETTER TO MY DOCTOR

This evening
the white blossoms
on my dogwood tree
cast hope
against the dark.
Because you believed me,
listened,
no guarantees
but no despair,
I trust you.

FRAN PORTLEY©
Mahwah, New Jersey

Lessons From the Practice

Stedman's

KATHLEEN BELL UNGER, MD
San Francisco, California

I REMEMBER the very first time that my old friend failed me, sometime in the late 1970s. The word was **nanogram**. I could not find it in my medical dictionary. It was inconceivable that it was not there. I rationalized away the failure of my *Stedman's Medical Dictionary.*

A few years went by, during which the dictionary appeared to function perfectly. Then it failed me again, on **dopamine**, and on **monoclonal antibody**. Giving false reassurance, it worked fine again—for a while—putting my fears to rest . . . well, almost to rest. I found myself writing little notes to myself, reminders to look up certain words, the next time that I was at the hospital medical library.

Some more time went by. Then, **alexithymia** happened, and **recurrence risk**. They started coming thick and fast now. My denial first showed cracks, then rapidly crumbled. I would have to get a new version of *Stedman's.*

I can clearly remember that September day back in 1965, when my freshman medical student self bought that first volume. It was by far the most expensive book I had ever purchased. If I had been asked about it, I would have said that it would serve me well, forever. After all, what was there new in medical terminology that could possibly be added? There had been nothing new added to *Gray's Anatomy*, had there? No new muscles or nerves or organs discovered, right? The concept of medical terminology as a living, growing thing had not yet occurred to me. After all, it was all based on Greek and Latin, wasn't it?

A few months ago, looking through a medical book catalogue, I noticed that they were offering a 25th edition of *Stedman's.* I became curious to see what edition my old one was and was shocked to see that it was the 20th. I wondered, uneasily, how the editors could have had enough new words to put out five more editions over a span of only 25 years. It was bittersweet to realize that a quarter of a century had gone by since that freshman year in medical school. A whole new generation of physicians had grown up. There really were new terms, new diseases. I had better become current posthaste.

When my new *Stedman's* arrived, it sat there, pristine in its unopened cellophane wrapper, for at least a month while I eyed it suspiciously. It was appreciably thinner than my old one, which I found alarming. (It was also an inch wider, which I failed to notice.) Then, **leu-enkephalin** came along, and I had to plunge in.

It proved to be an experience of pure pleasure. As I turned page after page, I felt as though I were reexperiencing a favorite childhood pastime, one of cruising through the pages of an encyclopedia, reading whatever caught my eye.

And there were so many things that caught my eye. Those meticulously etched drawings of anatomic structures were almost all gone. The type was darker, the page was whiter. Depictions of fetuses with rarely encountered congenital anomalies no longer graced its pages.

Other things were all there, every single new term—along with abbreviations, proper names, even federal facilities like the **Centers for Disease Control**. It was so complete that I was a little surprised to note that they did not include the CDC's phone number.

I am now at peace with the reality of medical dictionaries getting "degenerative arthritis," much like people do, and not merely of the "spine." Fortunately, this is a reversible disorder, at least in dictionaries.

My new *Stedman's* sits on my desk at home, where it is the most handy. I use it frequently, sometimes just for the fun of it. It continues to supply new knowledge, as well as to clarify formerly fuzzy concepts.

My old *Stedman's* sits in a place of honor, on a wall of bookshelves in our study. It is placed right next to my father's copy of *Gray's Anatomy* (23rd edition, 1936), which he passed on to me when I started medical school.

The following are taken from *Stedman's Medical Dictionary*, 25th edition, published in 1990:

alexithymia In psychopathology, a symptom describing difficulty in recognizing and defining one's emotions, defining them in terms of somatic sensations or behavioral reactions.

Centers for Disease Control (CDC) The federal facility for disease eradication, epidemiology and education headquartered in Atlanta, Georgia. It encompasses the Center for Infectious Diseases, Center for Environmental Health, Center for Health Promotion and Education, Center for Prevention Services, Center for Professional Development and Training, and Center for Occupational Safety and Health. Formerly named the Center for Disease Control (1970) and the Communicable Disease Center (1946). [The CDC's phone number is 404-639-3291.]

dopamine 3-Hydroxytyramine; decarboxylated dopa; in neurophysiology, an intermediate in tyrosine metabolism and precursor of norepinephrine and epinephrine in the central nervous system; its presence in the central nervous system and localization in the basal ganglia (caudate and lentiform nuclei) suggest that dopamine may have other functions.

leu-enkephalin In neurophysiology, one of the pentapeptide endorphins (opioid peptides), found in many parts of the brain, that bind to specific receptor sites, some of which may be pain-related opiate receptors; hypothesized as endogenous neurotransmitters and nonaddicting analgesics.

monoclonal antibody In immunochemistry, pertaining to an immune or protective protein from a single clone (colony of cells derived from a single cell by asexual reproduction) or genetically homogeneous population of hybrid cells, all molecules of which are the same. Hybrid cells are cloned to establish cell lines producing a specific monoclonal antibody.

nanogram A unit of weight measure used in SI units (Système International d'Unités) and in the metric system to signify one billionth of a gram (10^{-9}).

recurrence risk In genetics, meaning risk that a disease

(Unger KB: Stedman's. West J Med 1992 Mar; 156:324-325)

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Reprint requests to Kathleen Bell Unger, MD, 2000 Van Ness Ave, Suite 710-711, San Francisco, CA 94109.

will occur elsewhere in a pedigree, given that at least one member of the pedigree, the proband, exhibits the disease.

GENERAL REFERENCES

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Denying the Inevitable—The Misplaced Use of Technology

WILLIAM E. WATTS, MD
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DAVID T. WATTS, MD
Madison, Wisconsin

VAN WAS AN 88-year-old retired engineer who had been failing for months and, to some extent, for years. He was becoming progressively demented from multiple cerebral infarctions. Unfortunately, there was no treatable or reversible cause of his deterioration. He was widowed and had no children, so a niece was responsible for decisions and arrangements for his personal needs and medical care.

His internist, who had been Van's primary physician for many years, had a conference with the niece. Van's prognosis was discussed. The presence of significant multi-system disease and progressive neurologic decline meant that further decline and death were highly likely. The niece, however, was dissatisfied with this outlook. The internist was dismissed, and Van's care was transferred to a tertiary medical center. This center was a teaching institution of premier caliber with a full range of staff and equipment: subspecialists in nearly every conceivable discipline with access to a dazzling array of technological devices. An institution's preeminence in specialty expertise also can be its peril: a frail elderly patient risks becoming dehumanized, a set of diseases instead of a person. Controlling symptoms and providing palliation and comfort do not belong to any one specialty. (This reference to tertiary care centers is generic and is in no way intended to be disrespectful of the fine center where Van spent much of his last year. Nor is excessive medical meddling seen only in tertiary centers. Some physicians treat as long as there is a heartbeat, regardless of a patient's overall prognosis and quality of life.)

When first seen at the medical center, Van could no longer take care of himself, required aid in dressing and bathing, was falling repeatedly, asked the same questions again and again, was disoriented, frequently incontinent, and had lost 30 pounds. He did not know the date, the day of the week, or the name of the President. There is no evidence at any time during his last year of treatment at the center that he improved in any of these abilities. Instead, much of the time he was worse despite—or because of—all the invasions of medical technology.

During his last year he had three computed tomographic studies of his head, an electroencephalogram, a bone scan, a spinal tap, four chest x-ray films, two abdominal x-ray films, a renal ultrasound, an intravenous pyelogram, a retrograde pyelogram, many blood drawings with counts and chemistries, numerous urinalyses, blood and urine cultures, hair tested for arsenic, serum toxicology and heavy metal screens, urine toxicology.

He was in the hospital three times, for a total of 38 days. He was seen in consultation by neurologists, gastroenterologists, anesthesiologists, and urologists. He had a prostate resection. He was examined by many residents, along with countless assessments by dieticians, physical therapists, speech therapists, occupational therapists, and nurse specialists.

He had nasogastric tube feeding and indwelling catheters for months. Various forms of restraints were applied, including Posey, chest, and wrist restraints, body restraints, and hand and foot restraints. Why? Because he pulled out his IV lines and nasogastric tubes. He was given many parenteral solutions, three units of packed red cells, and one unit of whole blood.

At one point, a percutaneous gastrostomy was ordered, but his niece would not give her permission. She was becoming disenchanted with the lack of apparent benefits and the distressing nature of the treatments Van was receiving. She wanted his nasogastric tube removed and her uncle released from the hospital. Under pressure from the attending physician and an Ethics Committee representative, the niece relented. Later an order was written, "Please consult Dr B and Dr W (neurologist and physiatrist): Has this patient an incurable or irreversible condition? Please advise on continuation of nutritional support with respect to ultimate prognosis." Six months before this, the neurologist had written, "I believe his current situation offers no reasonable prospect of recovery."

After a 17-day hospital stay, Van was discharged with a nasogastric tube. Later he could be fed by mouth, but 24-hour nursing care was required. Shortly after his 89th birthday he was reported to be "remarkably better." In fact, he was so much better he was able to die a few weeks later. After nearly a year of modern medical care. Finally!

There are lessons to be learned from Van's terminal year. While modern medical centers can offer dramatic and amazing cures, these are less forthcoming to the chronically ill, debilitated, and demented. The interests of frail elderly persons are often better served by a humanitarian approach that recognizes the limitations of technology.

The niece's expectation of dramatic success led her to seek care at the tertiary center. But with that change there was a loss of perspective that can only be developed in a close personal relationship of many years. Thus, Van entered a system that knew little of who he was—a proud, independent, retired engineer.

To the system he was alternatively a diagnostic or therapeutic challenge, or a placement problem. Diagnostic testing searched for the crucial lesion (such as obstructing hydrocephalus, or arsenic poisoning) which would lead to a dramatic cure. The structure of the academic setting often obscured primary responsibility to the patient by involving multiple layers of housestaff and attending staff. Continuity

(Watts WE, Watts DT: Denying the inevitable—The misplaced use of technology. West J Med 1992 Mar; 156:325-326)

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was thwarted by rotation of responsibility at the different levels. This diffusion of responsibility was accentuated by the many specialists and allied health professionals who focused on only one organ or system. No one oversaw the thread of illness or appreciated its tragic proportions between the multiple hospital stays.

The atmosphere was generally aggressive in terms of diagnosis and treatment. The values and wishes of this confused elderly patient were ignored. He had no formal advance directive, and therefore nothing impeded the intensity of his treatment. The attitude, often implied if not stated, seemed to be, "We are experts in diagnosis and treatment, and that we will do." This attitude lacked a tempering influence by a physician skilled in the art of the possible.

The dollar costs of Van's terminal year were huge, many times the costs of his medical services for the rest of his 87 years. The real tragedy, however, was not the wastefulness but the indignity suffered by the patient. His dignity suffered as he became an object of technologic interventions. His physicians could not allow him to die. Nor could the Ethics Committee, which found him "neither comatose nor terminal," and therefore forbade removal of his feeding tube.

The primary care internist had seen this tragedy played out before and had foreseen the inevitable end. After Van's death the internist reviewed the medical record because of a legal challenge to the will. He said, "God, don't let them do that to me."

The Examination Room

GWEN L. NAGEL
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FRIDAY AFTERNOON I accompanied my husband, Jim, as he kept an appointment with his internist, Mike Levin. My plans for that afternoon had not included a trip to the medical office building at Newton-Wellesley Hospital, but because Jim had been limping around on a sore foot (a month ago something in his arch went "ping" as he made a heroic effort to save a point on the tennis courts), we both anticipated he might come home in a cast. Reluctantly I rode with Jim to the clinic, consoling myself that I would catch up on *People* or *Newsweek* in the waiting room.

But Jim wanted me to continue to stay by his side, so when Mike's receptionist ushered Jim into an examination room I followed. I didn't even have time to snatch a magazine from the table in the waiting room.

Once inside the small office, which was lit by glaring fluorescent lights, I peered wearily at two plastic models on display. One was a large replica of a human spine, its curve graceful, serpentine. The other was a squat plastic heart that, balanced as it was on a black metal rod, appeared to be skewered like some hunk of meat set aside for a barbeque. The colors of both models seemed garish to me, but since I have never seen the "real" thing I am guessing. White plastic nerves jutting out of the spine were unpleasantly reptilian, like the snakes on Medusa's head. I fidgeted on a black vinyl chair as Jim, from his perch on the examination table, swung his legs, the paper beneath him rustling with every slow arc of leg.

"Don't be alarmed," Jim said to me as he watched his swinging feet, "if my legs don't respond when Mike hits me with his rubber hammer. They never do."

"Never?"

"Never."

I turned my attention to something less grim: a large plastic container that sat on the table to my left. It looked like a fat, jovial cookie jar filled with what, through the opaque plastic, vaguely appeared to be golf tees, little round shapes in white, red, black, and yellow. Curious, I looked more carefully at what was inside the sealed jar. It was filled with used plastic syringes, each one carefully labeled with strips of typed numbers taped around the brightly colored shafts. A ghastly collection, the sinister gray needles evoked sickness and hospitals, dope and death, and, finally, long stretches of beaches littered with the refuse of used medical supplies.

I turned from this menacing jar to the walls of the office. There is usually a magazine stuffed in the hanging rack, but on this day it was empty. A collage on the wall across from me caught my attention. Two photographs were matted and framed with a page of print done by a child and entitled "Forsythia." I looked closer at the photographs. In one a little boy who bore some resemblance to Mike stood proudly at the controls of a power boat; in the other, his back to the camera, he dangled a fishing line into the water below. Next to these images were a few short lines presumably written by the same little boy. The letters, which sprawled upward to the right corner, were of varying sizes, and the "g" and "j" and "d" were all printed backward. This collage, which had been professionally matted and framed, gave evidence of a preserving spirit and parental pride. Assuming that some teacher one fine spring day had assigned her 2nd or 3rd grade class to write a poem about forsythia, I was not too eager to read the poem. I expected lots of references to the color yellow and bright spring days; I did not expect to find anything of much literary value from an eight-year-old. I read the poem.

Forsythia

in the night,
if you are asleep
And only if
you are asleep,
The stars jump
on the forsythia.

BY BEN LEVIN, 1989

I was astonished. I reread the poem, and this time I noticed that the letter "j" was turned around so "jump" appeared to be "lump." The handwriting error made me smile. I read the poem again, and by this time I noticed that Jim had read it too. We sat beaming at each other. Ben's six scrawled lines were marvelously unpredictable and captured a sense of wonder that good poems always do.

William Wordsworth once wrote he was "surprised by joy." I think I shall never forget the shot of joy Jim and I shared on a rainy, cold day in October as we, fearing bad news, sat amid the menacing accoutrements of our internist's examination room and learned from Ben's poem that sometimes at night the stars jump on the forsythia.

(Nagel GL: The examination room. West J Med 1992 Mar; 156:326)

Reprint requests to Gwen L. Nagel, 168 Red Fox Run, Athens, GA 30605.

(Continued from Page 266)

March 24-25—**Basic Training for Institution Review Board Members.** Sheraton Old Town, Albuquerque. Tues-Wed. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

March 25-26—**Ethics, Justice, and Tribal Participation in Research of American Indians.** Sheraton Old Town, Albuquerque. Wed-Thurs. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

March 27-28—**Healthcare Rationing: Who Decides?** Hilton Hotel, Albuquerque. Fri-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

April 2—**4th Annual Pharmacology Update.** Holiday Inn-Pyramid, Albuquerque. Thurs. Contact: Diane P. Atchinson, RN, CANP, MSN, PO Box 22569, Kansas City, MO 64113-0569. (816) 765-6644 or (800) 245-0372.

April 4—**Sleep Disorders Update.** Holiday Inn-Pyramid, Albuquerque. Sat. Contact: Mary Boning, Presbyterian Hospital, PO Box 26666, Albuquerque 87125-6666. (505) 841-1225.

April 9-12—**3rd National Meeting for State Cancer Pain Initiative.** Sheraton Old Town, Albuquerque. Thurs-Sun. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

April 10-11—**Wiggins Lectureship, Technology of Obstetrics and Gynecology: A New Approach to Old Problems.** Hilton Hotel, Albuquerque. Fri-Sat. Contact: Mary Boning, Presbyterian Hospital, PO Box 26666, Albuquerque 87125-6666. (505) 841-1225.

April 23-25—**14th Annual Cardiac Pulmonary Update.** Hyatt Regency Hotel, Albuquerque. Thurs-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

April 29-May 2—**Association of Veteran Administration Surgeons Annual Meeting.** Hilton Hotel, Albuquerque. Wed-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

April 29-May 2—**12th Annual UNM-ACP Emergency Medical Symposium.** Holiday Inn Pyramid, Albuquerque. Wed-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

May 14-15—**6th Annual Multicultural Mental Health Conference on Family and Children.** Hilton Hotel, Albuquerque. Thurs-Fri. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

May 15-16—**New Mexico Medical Society Annual Meeting.** The Marshall Building, Albuquerque. Fri-Sat. Contact: Glenn Taylor, New Mexico Medical Society, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

May 28-29—**3rd Annual Southwest Wound Care Symposium.** Holiday Inn-Pyramid, Albuquerque. Thurs-Fri. Contact: Diane Atchinson, PO Box 22569, Kansas City, MO 64113-0569. (816) 765-6644 or (800) 245-0372.

July 13-17—**Imaging 1992: Ultrasound, CT, MR, and Mammography.** Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 7-11—**Mammography Update.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

March 16-22—**Clinical Cardiac Electrophysiology Board Review** (Sponsor: UUSM). Mon-Sun. Snowbird. Contact: UUSM.

March 24-27—**Family Practice Refresher Course** (Sponsor: UUSM). Tues-Fri. Salt Palace, Salt Lake City. Contact: Leslie Munsee, (801) 581-7234.

June 21-27—**School on Alcoholism, Drug Dependencies** (Sponsor: UUSM). Sun-Sat. U of U Browning Auditorium. Contact: UUSM.

June 24-27—**Slice of Life: Interactive Video and Related Multimedia Technology in Health Education** (Sponsor: UUSM). Wed-Sat. U of U Eccles Genetics Auditorium. Contact: UUSM.

July 12-17—**Update in Internal Medicine Focus on Ambulatory Care Medicine** (Sponsor: UUSM). Sun-Fri. Snowbird. Contact: UUSM.

August 6-8—**ISLD Dental Congress** (Sponsor: UUSM). Tues-Sat. Marriott Hotel, Salt Lake City. Contact: UUSM.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.
WRI:	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

March 20—**Integrated Approach to the Dizzy Patient.** Seattle. Fri. Contact: VMMC.

March 22-25—**Urgent Problems in Primary Care.** Bend, Oregon. Sun-Thurs. Contact: Group Health, (206) 326-3441.

March 23-26—**Death Investigations.** Seattle. Mon-Thurs. Contact: U/W.

March 25—**Ethics Conference.** Seattle. Wed. Contact: VMMC.

March 25-27—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

(Continued on Page 328)

CONTINUING MEDICAL EDUCATION

(Continued from Page 327)

March 27-28—**Ophthalmology Annual Meeting.** Seattle. Fri-Sat. Contact: WAEPS, (206) 441-9762.

March 30-April 3—**Hawaii and CME.** Kauai, Hawaii. Mon-Fri. Contact: PCMS.

April 8-11—**General Practice Review.** Arizona. Wed-Sat. Contact: PNMEI, (206) 248-6322.

April 10—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

April 10—**Gastro-Esophageal Reflux: A Multi-faceted Disease.** Seattle. Fri. Contact: VMMC.

April 17-18—**Tacoma Surgical Club.** Tacoma. Fri-Sat. Contact: PCMS.

April 24—**Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

April 24-25—**Diabetes of the Eye.** Seattle. Fri-Sat. Contact: U/W.

April 24-25—**Low-Back Pain.** Seattle. Fri-Sat. Contact: VMMC.

April 30-May 2—**Musculoskeletal Disease.** Seattle. Thurs-Sat. Contact: U/W.

May 1-3—**Radiology Annual Meeting.** Seattle. Fri-Sun. Contact: PNWRS, (206) 441-9762.

May 6-9—**Emergency Physicians Annual Scientific Assembly.** Seattle. Wed-Sat. Contact: WACEP, (206) 441-9762.

May 8—**Office Procedures.** Tacoma. Fri. Contact: PCMS.

May 13-15—**Fifth Conference on Occupational Hazards to Health Care Workers.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 15-16—**Medical and Orthopedic Issues of Active and Athletic Women.** Seattle. Fri-Sat. Contact: VMMC.

May 16—**Infectious Disease in Primary Care.** Seattle. Sat. Contact: U/W.

May 21-22—**Cardiology Conference.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

May 27—**Pesticide Medicine.** Eastern Washington. Wed. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 30—**The Fetal Patient.** Seattle. Sat. Contact: VMMC.

June 11—**Endocrinology.** Everett. Thurs. Contact: PNMEI, (206) 258-6322.

June 22-23—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: PCMS.

June 26—**Sports Medicine.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

July 23-26—**Current & Emerging Issues in Cancer Pain.** Seattle. Thurs-Sun. Contact: U/W.

July 29-31—**STD Update.** Seattle. Wed-Fri. Contact: U/W.

August 21-22—**Regional CME Network Meeting.** Seaside, Oregon. Fri-Sat.

September 9-12—**Washington State Medical Association Annual Meeting.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 23-24—**Critical Care.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

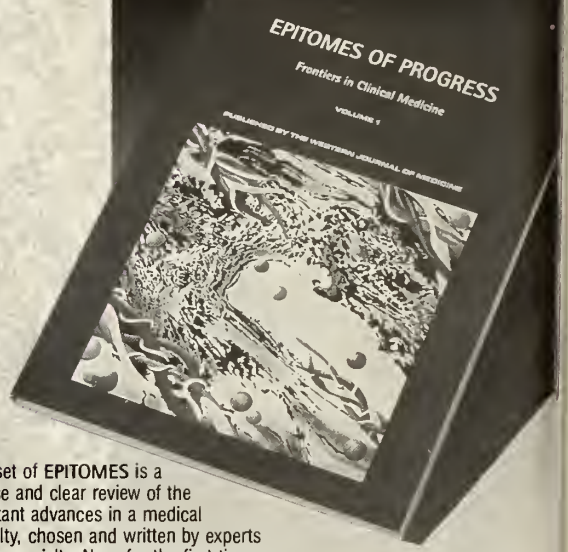
WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact. Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 11-13—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

epitome i-'pit-ə-mē\ *n* [L, fr. Gk *epitomē*, fr. *epitemnein* to cut short, fr. *epi-* + *temnein* to cut — more at TOME] (1520) **1 a** : a summary of a written work **b** : a brief presentation or statement of something **2** : a typical or ideal example: EMBODIMENT (the British monarchy itself is the ~ of tradition —Richard Joseph) **3** : Plural — *Epit-o-mes* — A regular FEATURE of *The Western Journal of Medicine*, now available in a single, bound volume.



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All positions offer competitive compensation packages. For additional information please send CV to **Jan Sturges, Medical Management Services, 532 Race St, San Jose, CA 95126.**

A FOUR PHYSICIAN OB/GYN DEPARTMENT of multispecialty group in San Jose, California seeks a fifth BC/BE OB/GYN to join their busy practice. Call schedule will be 1:6. Four-day work week. Competitive salary and benefits. Send CV to Jan Sturges, MMS, 532 Race St, San Jose, CA 95126-3432.

OB/GYN. 100-BED, FULL-SERVICE HOSPITAL located 30 miles south of San Jose seeks a BE/BC OB/GYN to establish a solo practice due to area's growth. This is an outstanding opportunity for a physician wanting to establish his/her own practice. Call coverage is available and a competitive financial package is being offered. For further information, call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

EXCELLENT OPPORTUNITY FOR BC/BE INTERNIST to join four Internists in San Jose area with future opportunity to assume practice of retiring physician(s). Exceptional income guarantee and benefit package being offered. Interested candidates call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

POSITIONS AVAILABLE FOR EMERGENCY PHYSICIANS WORKING PM SHIFTS. Hourly differential paid in addition to fee-for-service compensation. Shifts vary from seven to nine hours in length. Excellent fringe benefits. Malpractice paid. Contact Nancy C. Kendall at SPEMG, Inc, 8350 Auburn Blvd, Ste 100, Citrus Heights, CA 95610; or call (916) 727-1049 for more information.

BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

BC/8E GENERAL INTERNIST NEEDED. Nine physician department in 27 doctor multispecialty clinic. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

PHYSICIANS WANTED

PHYSICIAN OPPORTUNITIES NATIONWIDE
For all specialties for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **G & G Physician Services, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

INTERNIST/FAMILY PRACTITIONER. Join progressive and well respected community clinic in desirable San Francisco/Oakland bay area. Position available for Internist or Family Practitioner with strong Internal Medicine background. Limited call, 3.5-5 day work week; salary plus fee-for-service for inpatient care. Excellent fringe benefits which include malpractice insurance. Send CV to Pat Royball, Personnel, La Clinica de la Raza, 1515 Fruitvale, Oakland, CA 94601; (510) 534-0078.

INVASIVE AND/OR NONINVASIVE 8C/BE CARDIOLOGIST needed for well established private practice in Riverside, California. Salary guarantee. With partnership potential. Immediate opening available. Send CV to 3900 Sherman Dr, #B, Riverside, CA 92503, attn: Lynn.

INTERNAL MEDICINE. Internist, BC/BE, needed for well established private practice in Riverside, California. Salary guarantee. Immediate opening available. Send CV to 3900 Sherman Dr, #B, Riverside, CA 92503, attn: Lynn.

NEW MEXICO. Excellent opportunity for BC/BE OB/GYN, Internal Medicine, and Family Practice to join successful practices or start new in a growing community. Plan on full practice from the beginning. Enjoy sunshine, skiing, hiking, fishing, and hunting in a southwestern lifestyle. For further information on benefits and compensation contact Anne Winter, RN, Director of Professional Development, St Joseph Healthcare System, Albuquerque, NM; (505) 246-8003.

CALIFORNIA MEDICAL/LEGAL DISABILITY EVALUATIONS. Opportunities available in San Jose, San Ramon, Fremont, and Capitola, California for BC physicians in Orthopedics, Psychiatry, and Cardiology with multispecialty forensic medical evaluation group. Practice limited to evaluations. California license required. Excellent opportunity to supplement income. Send inquiry and CV to Martie Woodson, QMA, 2131 The Alameda, San Jose, CA 95126.

PHYSICIANS WANTED

PHYSICIANS NEEDED

The continuing growth of our service area population (now 105,000) has created an immediate need for additional BC/BE physicians in the following specialties:

- EMERGENCY MEDICINE
- FAMILY PRACTICE
- ORTHOPEDIC SURGERY
- OTOLARYNGOLOGY
- PEDIATRICS
- ONCOLOGY (some general Internal Medicine necessary initially)

These excellent practice opportunities offer guaranteed income and a strong referral base.

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 105,000; a growing area with new businesses and a stable economy. A 30% plus growth in population and jobs is predicted for our area during 1990s.

Located in central California near Sequoia National park, Tulare offers an excellent family oriented lifestyle and all expected amenities. Beautiful homes, close to hospital and office, are affordably priced. Good schools, many community activities, and abundant recreation including golf, tennis, skiing, mountain and equestrian activities. Easy access to all California's major metropolitan and resort areas.

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Tulare District Hospital
Physician Recruiting Office
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Los Angeles, CA 90009
(800) 468-2687

PEDIATRICIAN BC/BE for hospital-based teaching practice. Interest and training in Neonatology and Critical Care Pediatrics preferred. Join three full-time Pediatricians and two full-time Neonatologists in hospital with Community Level III NICN and busy inpatient and outpatient services. Paid malpractice. Salary negotiable based on training and experience. Submit CV and references to Leedell Reuben, MD, Director, Pediatrics/Neonatal Services, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201, (209) 468-6611. AA/EOE.

BC/BE FAMILY PHYSICIANS needed for large multispecialty group in San Jose, California. Continuing Care and Urgent Care available. Family Practice Department includes Internal Medicine, Pediatrics, Gynecology, minor surgery with inpatient/outpatient responsibilities. Good call coverage exists. Competitive salary and benefits offered. Call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

FAMILY PRACTICE, BC/BE to join group practice in growing southwestern town. Full service clinic, 280-bed hospital. Offering competitive salary, equal call schedule, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

(Continued on Page 330)

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PHYSICIANS WANTED

NORTHERN CALIFORNIA

San Jose's leading multispecialty group is growing. We are seeking BE/BC physicians in the following specialties:

- Orthopedic Surgery
- Internal Medicine/ General
- Physiatry
- Urgent Care
- Family Practice
- Otolaryngology
- Occupational Medicine
- Pediatrics

If you are committed to excellence and strongly motivated for success, we would like to hear from you. Please send your CV to Maureen Forrester, San Jose Medical Group, Inc, 45 S 17th St, San Jose, CA 95112; **or call (408) 282-7833.** An independent physician group affiliated with Stanford University Medical Center.

NORTHERN CALIFORNIA. BC/BE GENERAL INTERNIST sought in rural community. Solo practice with shared call schedule. Send CV to Number 257, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

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CALIFORNIA MULTISPECIALTY. Dermatologist, Radiologist, Otorhinolaryngologist, General Surgeon, Cardiologist, Internal Medicine, Pediatrician, Gastroenterologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

OB/GYN—Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE Physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

ORTHOPEDIC SURGEON. University of California, San Francisco seeks a BC/BE Orthopedic Surgeon to fill a faculty/staff position at the Valley Medical Center, Fresno. The Orthopedic Department at VMC supports a busy trauma service and actively participates in teaching residents in General Surgery, Emergency Medicine, and Family Practice. This position also offers private practice opportunities in a setting within the faculty group. Competitive salary and benefits. The central California location offers affordable and enjoyable year-round recreational living. Address inquiries and CVs to Louis Conway, MD, Acting Chief of Orthopedics, 4910 E Clinton, #101, Fresno, CA 93727. EO/AA employer, women and minorities are encouraged to apply.

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OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

INTERNIST/FAMILY PRACTITIONER—SAN FRANCISCO. This is an excellent opportunity for a BE/BC full-time or part-time practitioner to join our busy, established multispecialty practice. Large patient base, fee-for-service model, with well equipped lab, x-ray, and pharmacy. Highly competitive salary, extra for shared on-call, and excellent fringe benefit package including fully paid malpractice coverage, allowance and one week per year for CME, medical and dental insurances for physician and family, pension, short- and long-term disability, assistance with relocation expenses if needed, and parking. Close to major medical institutions. Research and teaching available at practice. Good work hours and quality lifestyle. Many cultural and recreational amenities. Fluency in Chinese highly desirable. Please send your CV to Linda Yu Bien, Assistant Director, North East Medical Services, 1520 Stockton St, San Francisco, CA 94133; or call work hours at (415) 391-9686. NEMS is an equal opportunity employer.

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PEDIATRICIANS—Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

BE/BC UROLOGIST to join busy 28 doctor multispecialty group practice. Excellent practice opportunity, full range of benefits, early partnership status. For more information contact Shane Spray, 1400 Kincaid Mount Vernon, WA 98273; (206) 428-2524.

NEPHROLOGIST WANTS PARTNER/ASSOCIATE BC/BE Gastroenterologist/Cardiologist/Nephrologist/Pulmonologist. Excellent practice, equal partnership opportunity without buy-in or overhead. Send CV to Dr. M. Streger, 27800 Medical Center Rd, Ste 122, Mission Viejo, CA 92691.

VASCULAR SURGEON—BC/BE, recently trained (university program preferred) for mixed Vascular and General Surgery group practice in San Francisco. Send CV and availability to A. Aronow, MD, 45 Castro St, San Francisco, CA 94114.

SOUTHERN CALIFORNIA. FAMILY PRACTICE, BC, energetic individual for a rapidly growing three physician practice. Will need to do clinic, hospital, and long term care facilities. Excellent compensation, rapid progression to partnership. Location is 10 minutes from the ocean in a fast growing area near Oceanside. Here is a chance to practice private medicine without bureaucratic problems. Call (619) 630-2422.

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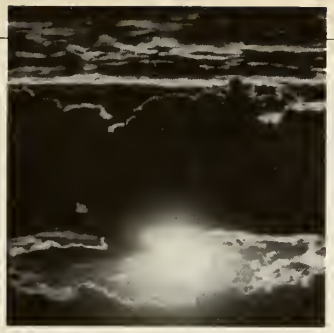

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(Continued from Page 330)

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AMBULATORY CARE, Hayward–Modesto, California Thriving practices, attractive facilities, competitive salary, profit-sharing, partnership with growth potential. Contact Robin Morgan, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612; (510) 835-7431. Outside of California, (800) 842-2619.

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OB/GYN NORTHERN CALIFORNIA. Join busy Primary Care group in picturesque alpine community. Excellent opportunity for GYN practice plus 100+ deliveries per year. This practice offers an exceptional professional, financial, and lifestyle opportunity. A slower pace allows for enjoyment of this mild four season area known for its wonderful outdoor recreation. A first year income guarantee, benefits, and interview and relocation expenses are offered. Call Kathie Powers at (800) 462-1857.

PHYSICIANS WANTED

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Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full-/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

BEAUTIFUL OREGON COAST. Private multispecialty cooperative with excellent facility seeking Family Practice physician to join five full-time Family Practitioners. Full spectrum of Family Practice. In-house lab, x-ray, day surgery. Contact Marce Knight, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294 or (800) 234-1231.

ANESTHESIOLOGIST, BC. Immediate half-time position in Pocatello, Idaho (50,000 population). Join four MDs and seven CRNAs. All specialties except Cardiac. Full benefit package. Excellent hunting, fishing, and skiing. Home of Idaho State University. Contact Philip J. Knox, MD; (208) 234-1363, 7727 Katsilometes, Pocatello, ID 83204.

HAWAII. INTERNIST AND PEDIATRICIAN NEEDED for rural underserved area. Full-time position in nonprofit community health clinic. Desire dedicated person to work in multicultural setting. Contact Kathy Garner, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-1458.

PHYSICIANS WANTED

WANTED: PHYSICIAN ADMINISTRATOR. NEW MEXICO. The Los Lunas Hospital and Training School, a 350-bed state operated facility for persons with developmental disabilities, is currently recruiting for a Physician Administrator. Located approximately 20 miles south of Albuquerque, New Mexico, we provide professional services and patient care to mentally and physically disabled clients. The job entails responsibility for general, technical direction of all service related to patient care and professional operations. Minimum qualifications include graduation from an accredited medical school and completion of an approved internship, plus four years experience in the practice of medicine, and licensure by the New Mexico Board of Medical Examiners. Salary up to $78,404 per year plus benefits; medical malpractice provided by the facility. Direct inquiries to David LaCourt, PhD, Administrator, Los Lunas Hospital and Training School, PO Box 1269, Los Lunas, NM 87031; (505) 841-5264.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

PEDIATRICIAN—NORTHERN CALIFORNIA. BC/BE Pediatrician needed in foothill community. Excellent opportunity for private practice. Competitive income guarantee. Send CV to Number 256, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Linda Johnson, 8009 S. 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

(Continued on Page 332)

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PHYSICIANS WANTED

MONTEREY BAY. Dynamic and cohesive medical community seeks Family Physician, Internist, and Pediatrician for group and/or independent practice. Plans for new 100-bed community hospital for 1994 with excellent and collegial medical staff. Unpretentious community, great for family, friendships, and lifestyle. For more information, please contact Ken Baker, President, at Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; FAX (415) 399-0411 or call (800) 229-0411.

MULTIDISCIPLINARY PAIN CENTER in Portland, Oregon seeks full-time physician, BC/BE Neurologist, Physiatrist, or Orthopedist, with interest in chronic pain, psychosocial aspects of medicine, working as part of a multidisciplinary team. Send CV to Janet E. Ploss, MD, Emanuel Pain Center and Worker Services, 3001 N Gantenbein, Portland, OR 97227; FAX (503) 280-4119.

MEDICAL GROUP seeks General Practitioner. Two Doctors of Chiropractic and one Doctor of Podiatric Medicine seek General Practitioner to join thriving group in Moreno Valley, California near Riverside. Town is fastest growing in US. Contact Dr Shapiro; (714) 924-0967.

NORTHERN CALIFORNIA—FAMILY PRACTICE FACULTY. Vigorous, growing program with rural emphasis, in Shasta-Cascade recreation area seeks residency trained BC/BE Family Physician to join core faculty team. Practice, teaching, and OB experience desirable. Responsibilities include teaching and direct patient care in hospital, FPC and coordination of R-1 curriculum. UC Davis affiliate program trains 18 residents in 254-bed regional referral center. Clean air, good schools, four-season recreation. Send CV to Perry Pugno, MD, Program Director, 2615 Breslauer Wy, Redding, CA 96001; (916) 246-5716.

PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (510) 601-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

GENERAL PHYSICIANS AND INTERNISTS— Physicians' salary to $70,020. Internists' (BE/BC) salary to $77,280. Western State Hospital is a fully accredited (JCAHO) and certified (HCFA) hospital. The hospital is associated with the University of Washington Medical School with clinical faculty appointment possible. A research institute, with the University, is now being developed. Western currently has a physicians' staff of 59, including 37 Psychiatrists and 22 other nonpsychiatric positions. Excellent benefits, including hospitalization/medical insurance, retirement, vacation estimated equivalence at 24%, plus optional deferred income plan. Send CV to Jerry L. Dennis, MD, Acting Medical Director, Western State Hospital, Fort Steilecoom, WA 98494; (206) 756-2349. EOE.

THE MEDICAL CENTER AT PRESCOTT, ARIZONA, is recruiting for a Physician, BC/BE in Internal Medicine or Family Practice for our outpatient department. The Medical Center is comprised of a 217-bed General Medical and Surgical Facility with a 68-bed Nursing Home Care Unit and a 208-bed Domiciliary. We have a staff of approximately 600 employees. Prescott is located in the mountains of north-central Arizona with a population of 25,000. Salary range is $71,000 to $83,000 depending on qualifications. Send CV to Rita Heidisch, MD, Acting Chief of Staff, VA Medical Center, Prescott, AZ 86313; or call (602) 776-6009. An equal opportunity employer.

PHYSICIANS WANTED

NORTHERN CALIFORNIA-FACULTY INTERNIST. Vigorous, growing Family Practice residency with rural emphasis in Shasta-Cascade recreation area seeks residency trained BC/BE Internist to join core faculty team. Practice and teaching experience desirable. Responsibilities include teaching and direct patient care in hospital and clinic. Clinical research encouraged. UC Davis affiliate program trains 18 residents in 254-bed regional referral center. Clean air, good schools, four-season recreation. Send CV to Perry A. Pugno, MD, Program Director, 2615 Breslauer Wy, Redding, CA 96001; (916) 246-5716.

MD NEEDED. Family Physician to join a 30 physician group. Benefits include four-day work week, three weeks paid vacation the first year, 1.25 days sick leave per month, six paid holidays and three paid floating holidays per year, malpractice paid, term life, health and dental insurance. CME, moving expenses, and pension plan also available. Call or send CV to Inland Empire Personnel Service, Mike Nation, Physician Placement Director, N 4407 Division, Ste 500, Spokane, WA 99207; (509) 484-3266.

INTERNIST. BE/BC Internist wanted as associate for solo practitioner in San Luis Obispo County. Growing medical community offering a tremendous quality of living; award winning local wineries, recreational lakes and beautiful oak-studded hillsides. Income guarantee. Contact Steven J. McAllen, MD, 959 Las Tablas Rd, Ste B2, Templeton, CA 93465; phone (805) 434-1166.

SAN JOSE. Family Physician for 200-bed hospital affiliated Primary Care group. The practice is located within one hour of beaches, mountains, and San Francisco. Salary plus incentives or guarantee with partnership in two years. For more information, please contact Ken Baker, President, at Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; FAX (415) 399-0411 or (800) 229-0411.

Managing Physician / Medical Affairs

The Hyland Division of Baxter Healthcare Corporation, a world leader in the production of both plasma and biotechnology-derived therapeutics, seeks a licensed physician with strong clinical and research orientation and effective managerial skills.

This individual will implement and maintain the adverse reaction monitoring system; review documents for medical content prior to submission to regulatory agencies and academic bodies; provide professional guidance and supervision on clinical research projects; and supply medical and clinical advise to other departments, especially Marketing, Regulatory Affairs, and Laboratory Research. In addition, the selected candidate will establish new areas for worldwide marketing and sales by identifying and developing important clinical market segments and new areas for clinical research.

At least 3 years experience in infectious disease and/or immunology is required. Industry experience helpful.

Employment is contingent upon the result of a drug screening test. For immediate consideration, please send your resume to: **Baxter Hyland Division, Human Resources Dept. BF/MP, 315 Arden Ave., Suite 23, Glendale, CA 91203.** An Affirmative Action/Equal Opportunity Employer.

Hyland Division

Baxter

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NTRODUCING ONCE-A-DAY

Zoloft™

(sertraline HCl) 50 mg, 100 mg scored tablets

GETS DEPRESSED PATIENTS BACK INTO THE MAINSTREAM

ZOLOFT: A New Choice in Antidepressant Therapy

- A new selective serotonin reuptake inhibitor—chemically distinct from all other antidepressants
- Effective in the treatment of depression
- Once-daily dosing—can be taken in the morning or evening, with or without food
- Available in 50-mg and 100-mg scored tablets for flexible dosing

The most common side effects include nausea, diarrhea or loose stools, tremor, insomnia, somnolence, and dry mouth.

Please see brief summary of prescribing information on adjacent page.

NEW ONCE-A-DAY

Zoloft™

(sertraline HCl) 50 mg, 100 mg scored tablets

From Depression...Into the Mainstream

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ONCE-A-DAY

Zoloft™

(sertraline HCl) 50 mg, 100 mg scored tablets

BRIEF SUMMARY

ZOLOFT™ (sertraline HCl)

INDICATIONS AND USAGE: ZOLOFT (sertraline hydrochloride) is indicated for the treatment of depression.

CONTRAINDICATIONS: None known. **WARNINGS: In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that ZOLOFT (sertraline hydrochloride) not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI.** **PRECAUTIONS** ***General:*** **Activation of Mania/Hypomania** - During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT (sertraline hydrochloride) treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants. **Weight Loss** - Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss. **Seizure** - ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. Accordingly, like other antidepressants, ZOLOFT should be introduced with care in epileptic patients. **Suicide** - The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Weak Uricosuric Effect** - ZOLOFT is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown, and there have been no reports of acute renal failure with ZOLOFT. **Use in Patients with Concomitant Illness** - Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses. ZOLOFT has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received ZOLOFT in double-blind trials were evaluated and the data indicate that ZOLOFT is not associated with the development of significant ECG abnormalities. ZOLOFT is extensively metabolized by the liver. The pharmacokinetics of ZOLOFT have not been studied in patients with significant hepatic dysfunction nor have patients with significant hepatic dysfunction been evaluated during treatment with ZOLOFT. Accordingly, ZOLOFT should be used with caution in such patients. Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until the pharmacokinetics of ZOLOFT have been studied in patients with renal impairment and until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with ZOLOFT, it should be used with caution in such patients. **Interference with Cognitive and Motor Performance** - In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. ***Information for Patients:*** Physicians are advised to discuss the following issues with patients for whom they prescribe ZOLOFT: Patients should be told that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol in depressed patients is not advised. Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast-feeding an infant. ***Laboratory Tests:*** None. ***Drug Interactions:*** **Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins** - Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT (sertraline hydrochloride) to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound ZOLOFT by other tightly bound drugs. In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either ZOLOFT (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for ZOLOFT compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the ZOLOFT group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped. **CNS Active Drugs** - In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in T_{max} for desmethyldiazepam in the ZOLOFT group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown. In a placebo-controlled trial in normal volunteers, the administration of two doses of ZOLOFT did not significantly alter steady-state lithium levels or the renal clearance of lithium. Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose. The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZOLOFT and such drugs is required. **Hypoglycemic Drugs** - In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. ZOLOFT administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown. **Atenolol** - ZOLOFT (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol. **Microsomal Enzyme Induction** - Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In clinical studies ZOLOFT was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism. **Electroconvulsive Therapy** - There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT. **Alcohol** - Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol in depressed patients is not recommended. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg in mice (10 times on a mg/kg basis and the same on a mg/m^2 basis as the maximum recommended human dose) and at doses up to 40 mg/kg in rats (10 times on a mg/kg basis and 2 times on a mg/m^2 basis, the maximum recommended human dose). There was a dose-related increase in the incidence of liver adenomas in male mice receiving sertraline at 10-40 mg/kg. No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was no increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg; this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg compared to placebo controls, this effect was not clearly drug related. Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes. A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (20 times the maximum human dose on a mg/kg basis and 4 times on a mg/m^2 basis). ***Pregnancy—Pregnancy Category B:*** **Teratogenic Effects** - Reproduction studies have been performed in rats and rabbits at doses up to approximately 20 times and 10 times the maximum daily human mg/kg dose (4 to 4.5 times the mg/m^2 dose), respectively. There was no evidence of teratogenicity at any dose level. At doses approximately 2.5-10 times the maximum daily human mg/kg dose, sertraline was associated with delayed ossification in fetuses, probably secondary to effects on the dams. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Non-teratogenic Effects** - There was also decreased neonatal survival following maternal administration of sertraline at doses as low as approximately 5 times the maximum human mg/kg dose. The decrease in pup survival was shown to be most probably due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown. **Labor and Delivery** - The effect of ZOLOFT on labor and delivery in humans is unknown. **Nursing Mothers** - It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman. **Pediatric Use** - Safety and effectiveness in children have not been established. **Geriatric Use** - Several hundred elderly patients have participated in clinical studies with ZOLOFT. The pattern of adverse reactions in the elderly was similar to that in younger patients. **ADVERSE REACTIONS** ***Commonly Observed:*** The most commonly observed adverse events associated with the use of ZOLOFT (sertraline hydrochloride) and not seen at an equivalent incidence among placebo-treated patients were: gastrointestinal complaints, including nausea, diarrhea/loose stools and dyspepsia; tremor; dizziness; insomnia; somnolence; increased sweating; dry mouth; and male sexual dysfunction (primarily ejaculatory delay). ***Associated with Discontinuation of Treatment:*** Fifteen percent of 2710 subjects who received ZOLOFT in premarketing multiple dose clinical trials discontinued treatment due to an adverse event. The more common events (reported by at least 1% of subjects) associated with discontinuation included agitation, insomnia, male sexual dysfunction (primarily ejaculatory delay), somnolence, dizziness, headache, tremor, anorexia, diarrhea/loose stools, nausea, and fatigue. ***Incidence in Controlled Clinical Trials:*** The table that follows enumerates adverse events that occurred at a frequency of 1% or more among ZOLOFT patients who participated in controlled trials comparing titrated ZOLOFT with placebo. Most patients received doses of 50 to 200 mg per day.

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials*

Adverse Experience	ZOLOFT (N=861)	Placebo (N=853)
	(Percent of Patients Reporting)	
Autonomic Nervous System Disorders		
Mouth Dry	16.3	9.3
Sweating Increased	8.4	2.9
Cardiovascular		
Palpitations	3.5	1.6
Chest Pain	1.0	1.6
Central and Peripheral Nervous System Disorders		
Headache	20.3	19.0
Dizziness	11.7	6.7
Tremor	10.7	2.7
Paresthesia	2.0	1.8
Hypaesthesia	1.7	0.6
Twitching	1.4	0.1
Hypertonia	1.3	0.4
Disorders of Skin and Appendages		
Rash	2.1	1.5
Gastrointestinal Disorders		
Nausea	26.1	11.8
Diarrhea/Loose Stools	17.7	9.3
Constipation	8.4	6.3
Dyspepsia	6.0	2.8
Vomiting	3.8	1.8
Flatulence	3.3	2.5
Anorexia	2.8	1.6
Abdominal Pain	2.4	2.2
Appetite Increased	1.3	0.9
General		
Fatigue	10.6	8.1
Hot Flushes	2.2	0.5
Fever	1.6	0.6
Back Pain	1.5	0.9
Metabolic and Nutritional Disorders		
Thirst	1.4	0.9
Musculoskeletal System Disorders		
Myalgia	1.7	1.5
Psychiatric Disorders		
Insomnia	16.4	8.8
Sexual Dysfunction-Male (1)	15.5	2.2
Somnolence	13.4	5.9
Agitation	5.6	4.0
Nervousness	3.4	1.9
Anxiety	2.6	1.3
Yawning	1.9	0.2
Sexual Dysfunction-Female (2)	1.7	0.2
Concentration Impaired	1.3	0.5
Reproductive		
Menstrual Disorder (2)	1.0	0.5
Respiratory System Disorders		
Rhinitis	2.0	1.5
Pharyngitis	1.2	0.9
Special Senses		
Vision Abnormal	4.2	2.1
Tinnitus	1.4	1.1
Taste Perversion	1.2	0.7
Urinary System Disorders		
Micturition Frequency	2.0	1.2
Micturition Disorder	1.4	0.5

*Events reported by at least 1% of patients treated with ZOLOFT are included.
(1) - % based on male patients only: 271 ZOLOFT (primarily ejaculatory delay) and 271 placebo patients.
(2) - % based on female patients only: 590 ZOLOFT and 582 placebo patients.

Other Events Observed During the Premarketing Evaluation of ZOLOFT (sertraline hydrochloride): During its premarketing assessment, multiple doses of ZOLOFT were administered to approximately 2700 subjects. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section. **Autonomic Nervous System Disorders**—*Infrequent:* flushing, mydriasis, increased saliva, cold clammy skin; *Rare:* pallor. **Cardiovascular**—*Infrequent:* postural dizziness, hypertension, hypotension, postural hypotension, edema, dependent edema, periorbital edema, peripheral edema, peripheral ischemia, syncope, tachycardia; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, varicose veins. **Central and Peripheral Nervous System Disorders**—*Frequent:* confusion; *Infrequent:* ataxia, abnormal coordination, abnormal gait, hyperesthesia, hyperkinesia, hypokinesia, migraine, nystagmus, vertigo; *Rare:* local anesthesia, coma, convulsions, dyskinesia, dysphonia, hyporeflexia, hypotonia, ptosis. **Disorders of Skin and Appendages**—*Infrequent:* acne, alopecia, pruritus, erythematous rash, maculopapular rash, dry skin; *Rare:* bullous eruption, dermatitis, erythema multiforme, abnormal hair texture, hypertrichosis, photosensitivity reaction, follicular rash, skin discoloration, abnormal skin odor, urticaria. **Endocrine Disorders**—*Rare:* exophthalmos, gynecomastia. **Gastrointestinal Disorders**—*Infrequent:* dysphagia, eructation; *Rare:* diverticulitis, fecal incontinence, gastritis, gastroenteritis, glossitis, gum hyperplasia, hemorrhoids, hiccup, melena, hemorrhagic peptic ulcer, proctitis, stomatitis, ulcerative stomatitis, tenesmus, tongue edema, tongue ulceration. **General**—*Frequent:* asthenia; *Infrequent:* malaise, generalized edema, rigors, weight decrease, weight increase; *Rare:* enlarged abdomen, halitosis, otitis media, aphthous stomatitis. **Hematopoietic and Lymphatic**—*Infrequent:* lymphadenopathy, purpura; *Rare:* anemia, anterior chamber eye hemorrhage. **Metabolic and Nutritional Disorders**—*Rare:* dehydration, hypercholesterolemia, hypoglycemia. **Musculoskeletal System Disorders**—*Infrequent:* arthralgia, arthrosis, dystonia, muscle cramps, muscle weakness; *Rare:* hernia. **Psychiatric Disorders**—*Infrequent:* abnormal dreams, aggressive reaction, amnesia, apathy, delusion, depersonalization, depression, aggravated depression, emotional lability, euphoria, hallucination, neurosis, paranoid reaction, suicide ideation and attempt, teeth-grinding, abnormal thinking; *Rare:* hysteria, somnambulism, withdrawal syndrome. **Reproductive**—*Infrequent:* dysmenorrhea (2), intermenstrual bleeding (2); *Rare:* amenorrhea (2), balanoposthitis (1), breast enlargement (2), female breast pain (2), leukorrhea (2), menorrhagia (2), atrophic vaginitis (2).

(1) - % based on male subjects only: 1005; (2) - % based on female subjects only: 1705.

Respiratory System Disorders—*Infrequent:* bronchospasm, coughing, dyspnea, epistaxis; *Rare:* bradypnea, hyperventilation, sinusitis, stridor. **Special Senses**—*Infrequent:* abnormal accommodation, conjunctivitis, diplopia, earache, eye pain, xerophthalmia; *Rare:* abnormal lacrimation, photophobia, visual field defect. **Urinary System Disorders**—*Infrequent:* dysuria, face edema, nocturia, polyuria, urinary incontinence; *Rare:* oliguria, renal pain, urinary retention. **Laboratory Tests:** In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation. ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance. **DRUG ABUSE AND DEPENDENCE** ***Controlled Substance Class:*** ZOLOFT (sertraline hydrochloride) is not a controlled substance. ***Physical and Psychological Dependence:*** ZOLOFT has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. However, the premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. As with any new CNS active drug, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of ZOLOFT misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior). **OVERDOSAGE** ***Human Experience:*** There have been 3 cases of ZOLOFT (sertraline hydrochloride) overdosage (approximately 750-2,100 mg). No specific therapy was required for any of the 3 patients, all of whom recovered completely. ***Management of Overdoses:*** Establish and maintain an airway, insure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. There are no specific antidotes for ZOLOFT. Due to the large volume of distribution of ZOLOFT, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

Pfizer

Roerig
Pratt
Pharmaceutical

(Continued from Page 332)

PHYSICIANS WANTED

TRINIDAD, CALIFORNIA

Private Indian clinic overlooking ocean on northern California coast seeking two BC/BE Family Physicians to join two other Family Physicians. Exciting, challenging, comprehensive program, including Obstetrics. Gael Dougherty, RN, Medical Department Coordinator, UIHS, PO Box 420, Trinidad, CA 95570; (707) 677-3693.

GENERAL INTERNIST. The VA Medical Center Long Beach, California, is recruiting for a Staff Physician. Duties include seeing patients in the Walk-in Clinic, supervision, and teaching of housestaff in the clinic. The VA is affiliated with the College of Medicine at the University of California, Irvine. Vacancy is full-time position, 40 hours/week. US citizenship is required. Please send CV to David Webb, MD, Associate Chief of Staff, Ambulatory Care (153), VA Medical Center, 5901 E 7th St, Long Beach, CA 90822. The VA is an Equal Opportunity Employer.

FULL-TIME PAY/PART-TIME WORK. 116K plus two weeks on, 2 weeks off, malpractice, and overhead paid. Churchill Community Hospital in Fallon, Nevada is looking for an Emergency Room Physician to work a block schedule. ACLS, ATLS, Primary Care BE. 10,000 patients per year serving one large rural area. Located 60 miles east of Reno and the Lake Tahoe area. Other practice opportunities also available. Contact Betty Kuffel, MD, ED, or Jeffrey Feike, Administrator; (702) 423-3151.

SAN FRANCISCO BAY AREA. Palo Alto Medical Clinic, a 150 physician multispecialty group with a national reputation for innovation and excellence, seeks BC/BE Family Practice physician to join vigorous eleven member department. Exciting opportunity for energetic person to become part of innovative health care team. Competitive salary based on experience. Excellent benefits package. Two year partnership track. Please forward letter of interest and CV to George Perlstein, MD, Medical Director, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

PUGET SOUND. Internist to share equipment, office, and call in high growth community 30 minutes north of Seattle. We seek a fourth physician eager to maintain independent practice and finances, to share expenses and reduce starting costs by first year use of computer, phone, ECG, etc. Buy in later. Ample patient base. Excellent medical community and full service hospitals. Maximal scheduling freedom, but would make own practice management decisions. Well located new office. Contact J. Shaw, MD, 1330 Rockefeller, Ste 210, Everett, WA 98201.

CALIFORNIA. The Sacramento Children's Medical Clinic, an ambulatory private practice for children of low income parents, consisting of four offices (one on wheels) needs a BE/BC General Pediatrician. Direct patient care and supervising midlevels for inner city, migrant health and outreach programs. Monday through Friday. Quake-free locale. Spectacular climate. Innumerable recreational opportunities. Competitive salary with equity potential. Contact Gilbert Simon, MD, 1355 Florin Rd, Ste 14, Sacramento, CA 95822, (916) 422-6326.

BC/BE Pediatrician needed for after hours clinic, Maricopa Medical Center. This opportunity emphasizes resident and medical student teaching as well as direct patient care in a setting providing both primary and tertiary care to an indigent population. Part-/full-time positions available. Contact Mary Rimsza, MD, Pediatrics, Maricopa Medical Center, PO Box 5099, Phoenix, AZ 85010.

NEED ASSOCIATE to join busy dermatology practice in Santa Barbara, California. Will also consider sale at a reasonable price. Excellent opportunity to live in a beautiful seaside community. Call Dr Senn at (805) 569-0186 or evenings at (805) 565-3908.

(Continued on Page 334)

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AIR FORCE

(Continued from Page 333)

PHYSICIANS WANTED

CENTRAL CALIFORNIA

BC/BE General Internist to join well established group of six BC Internists, five with subspecialties, in community 20 miles from the ocean. Seek well trained Internist desiring to provide comprehensive quality care in well equipped office with quality lab, x-ray, and diagnostic facilities. Interest in competence in critical care is important. The office is across the street from a progressive 220 bed hospital. Salary with bonus opportunity first year with partnership in two years. Reasonable call schedule. Excellent situation for the right physician. Send CV to Number 249, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NATIONWIDE TRAVEL. Health research organization seeks physician for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individual will be part of a large medical team conducting health examinations in government mobile exam centers traveling to 88 areas of the US through 1993. Must be licensed in one state. One year minimum commitment and full-time continuous travel required. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline, (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD, EOE/M/F/V/H.

PEDIATRICIANS. Excellent practice opportunities available in a Seattle, Washington suburb, Reno and Las Vegas, Nevada and southern California. For details, call Eloise Gusman; (800) 535-7698, or send CV to PO Box 101656, Fort Worth, TX 76185.

PHYSICIANS WANTED

SEATTLE/FACTORIA. An excellent opportunity exists for a three quarter to full-time BE/BC Family Practitioner to join the rapidly growing Providence Medical Care Center in Bellevue. This is an attractive, four year old facility in the high growth Factoria area. The center is located at the I-405/I-90 Interchange making it convenient for patients traveling from Seattle, Bellevue, Issaquah, and Renton. The practice provides Family Medicine, Internal Medicine, Orthopedics, Cardiology, and Hematology services. The ideal candidate will practice the full spectrum of family medicine, including Obstetrics. A competitive compensation package with a guaranteed base and benefits is being offered. Seattle is known as a beautiful area with many cultural events and recreational opportunities. The Medical Care Center is affiliated with Providence Medical Center, a 370 plus-bed teaching hospital in Seattle, Washington. For more information contact Sandra Kozlowski, Providence Medical Center, 500 17th Ave, C-34008, Seattle, WA 98124; (206) 320-2039.

WANTED: CLINICIAN/TEACHER to join 15 General Internists at Santa Clara Valley Medical Center and Clinics, a public hospital affiliated with Stanford University. Applicants should be BE (BC if eligible more than two years), love clinical medicine and patient care, enjoy housestaff and medical students, and have excellent sense of humor to deal with usual politics of university-affiliated public hospital/clinic work. Send inquiries, CV to Kent Imai, MD, Chief, Primary Care Division, Department of Medicine, Santa Clara Valley Medical Center, 750 S Bascom Ave, San Jose, CA 95128.

INTERNAL MEDICINE RESIDENCY POSITIONS—R2 level. Available July, 1992. Excellent teaching with ample ambulatory opportunities. Inquire with CV to Stanton Siu, MD, or Denise Flaherty, MD, Medical Education, Kaiser Hospital, 280 W MacArthur Blvd, Oakland, CA 94611; or call (510) 596-6126.

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BC/BE FAMILY PRACTITIONER for satellite clinic of prestigious multispecialty group practice. Join one other Family Practitioner and one Physician's Assistant in small town setting with urban culture 20 minutes away. Generous benefit package. Send CV to Donald Benz, MD or Karen Stanton, The Vancouver Clinic Inc, PS, 700 NE 87th Ave, Vancouver, WA 98664; (206) 254-1240.

PREVENTIVE MEDICINE RESIDENCY candidates sought. Two year program includes MPH degree and practicum leading to BE in General Preventive Medicine. Especially interested in individuals with in-skill development for health promotion and disease prevention for medically underserved populations. Boards in Internal Medicine/Family Practice/Pediatrics desired but not necessary. Salary $30,000 plus fringes. Please write/call Kevin Patrick, MD, MS, Director, University of California, San Diego—San Diego State University General Preventive Medicine Residency Program. San Diego State University, San Diego, California 92182-0567; or phone (619) 594-5332 or FAX to (619) 594-5613.

INTERNAL MEDICINE/FAMILY PRACTICE. Several HIV specialty practice opportunities available. Send CV and availability to A. Aronow, MD, 45 Castro St, San Francisco, CA 94114.

HEMATOLOGIST/IMMUNOLOGIST—BC/BE, recently trained (university program preferred), to join busy Oncologist in San Francisco. Send CV and availability to A. Aronow, MD, 45 Castro St, San Francisco, CA 94114.

INTERNAL MEDICINE/PRIMARY CARE—BC/BE, recently trained (university program preferred) for group practice in San Francisco. Send CV and availability to A. Aronow, MD, 45 Castro St, San Francisco, CA 94114.

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PHYSICIANS WANTED

GREAT OPPORTUNITIES IN NORTHERN CALIFORNIA

We're San Jose's leading multi-specialty private group practice with nine locations, and seek BC/BE physicians with broadly based high level training to **join our Department of Urgent Care and General Medicine.**

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The South Bay area provides a wide range of cultural and recreational activities, good schools, fine dining, and a congenial climate.

If you are committed to excellence and strongly motivated for success, we'd like to hear from you. Send your CV to Maureen Forrester, San Jose Medical Group,* 45 S 17th St, San Jose, CA 95112; or **call (408) 282-7833.**

*An independent physician group affiliated with Stanford University Medical Center

UROLOGISTS—BC/BE needed for multispecialty group practice in central California and single-specialty group in Tucson, Arizona. Excellent compensation packages and partnership opportunity. All inquiries confidential. Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

SEATTLE—OB/GYN. Join multispecialty group located 45 minutes south of Seattle. Practice provides affiliation with two premier northwest hospitals, one with level III nursery, 24 hour OB Anesthesiology, Neonatology physician support plus Neonatal ICU. One in four call provides ample time to enjoy the beautiful Pacific Northwest's cultural and recreational opportunities. Call Kathie Powers at (800) 462-1857.

SOUTHERN CALIFORNIA. Opportunity for part-time Emergency/Family Practice physicians at urgent care/industrial center in Orange. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled Family Practice physician to join our highly respected Urgent/Primary Care group with two beautiful Santa Cruz clinics. Flexible scheduling and a comprehensive benefit package. Rapid advancement to full partnership. Please send CV to Stuart Simon, MD, 6800 Soquel Dr, Aptos, CA 95003 and call (408) 662-3611.

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SEATTLE/TACOMA. As a Family Practitioner in this 26 physician group, you have the professional benefits of a group and the personal advantages of production/incentive based income. We can't find anything wrong with this picture! Unlimited income, quality reputation, time off and a call schedule allowing time for family, friends, hiking, biking and the great outdoors. For more information, please contact Ken Baker, President, at Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111. FAX: (415) 399-0411; (800) 229-0411.

NORTHERN CALIFORNIA RECREATION AREA. Multispecialty group has immediate opening for an Internal Medicine practitioner with a particular interest in Critical Care. Clinical activities involve full range of Internal Medicine outpatient and inpatient practice. Beautiful northern California location offers abundant recreational opportunities as well as small town living. Competitive salary and comprehensive benefit package. Please send CV to PO Box 8247, Truckee, CA 96162.

PHYSICIANS WANTED

FOURTH INTERNIST/FAMILY PRACTICE MD for well loved multidisciplinary health center part of east San Francisco bay area community clinic network. 24 plus clinic hours plus share hospital call and coverage. Resident teaching and UCSF clinical affiliation possible. Call (510) 644-6060.

SEATTLE, WASHINGTON. PACIFIC MEDICAL CENTER has Family Practitioner positions, BC/BE, available at three of its six neighborhood clinics. PMC is a growing, Primary Care-based, multispecialty organization with extremely well run, well equipped clinics that provide many ancillary services. Most of the clinics are located within one mile of a major hospital. PMC offers its providers a balanced life-style, competitive salaries, and an excellent benefit package that includes paid malpractice. The greater Seattle area offers year-round outdoor recreation including, skiing (snow/water), hiking, boating, and fishing at numerous lakes, national parks, and in Puget Sound. Send CV to Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4100.

CALIFORNIA, PACIFIC NORTHWEST, ARIZONA. Positions in Family Practice, Internal Medicine, Orthopedics, Pediatrics and OB/GYN. Call or send confidential CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

PHYSICIANS. Los Angeles County Department of Health Services is seeking full-/part-time BC/BE physicians for the following specialty: OB/GYN. Competitive salary, excellent benefits and malpractice insurance. Send CV to Mary Abbott, MD, H. Claude Hudson Comprehensive Health Center, 2829 S Grand Ave, Los Angeles, CA 90007; (213) 744-3750. Equal Opportunity Employer M/F.

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PHYSICIANS WANTED

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Northwest Permanente, P.C., a stable, multispecialty group serving 380,000 members of Kaiser Permanente in the Northwest Region, has a 1-year locums tenens position for a BC/BE family physician in our Urgent Care clinic. Practice includes 3 or 4 evenings/ week in urgent care setting with scheduled time in daytime trauma clinic. No weekend coverage or inpatient responsibilities required.

In addition to a professionally stimulating environment, we offer a competitive salary plus professional liability coverage, family medical insurance and paid time off. **Forward CV to: Fred M. Nomura, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn St., Suite 300, Portland, OR 97210-5398. EOE.**

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NORTHERN CALIFORNIA. Seeking full-time BC/BE Family Practitioner for The Permanente Medical Group satellite clinic in Fairfield. Become a member of our enthusiastic Family Practice department in this rapidly expanding northern California community located only one hour from San Francisco or Sacramento. Outpatient and inpatient responsibilities; limited night and weekend call. Excellent salary and benefits. Contact Gordon Leung, The Permanente Medical Group, Inc., Physician Recruitment Services, 1814 Franklin, 4th Floor, Oakland, CA 94612-3497; or call (800) 777-4912 or (510) 987-4949. EOE.

NORTHERN CALIFORNIA'S NUMBER ONE IMMEDIATE CARE medical center is currently seeking a motivated physician with Emergency/Family Practice experience to join our team. A college town, very attractive compensation, and location, are just a few of the things that make this position unbeatable. Please contact Francine Marquis; (916) 891-1676.

THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO and the Central California Faculty Medical Group seek a staff Cardiologist to join the teaching faculty at their affiliate, Valley Medical Center of Fresno. Applicants should be BC/BE. Full invasive and noninvasive cardiology services are available. In addition to the academic participation, there is potential for private practice experience. Geographic location offers a large population with a variety of cardiological disease. VMC has 350 active beds and conducts residency training programs in most major clinical disciplines as well as a fully accredited cardiology fellowship. The central California location offers enjoyable and affordable California living. Competitive salary and benefits. UCSF is an equal opportunity employer. Address inquiries to Lauren Grayson, MD, Chief of Cardiology, CCFMG, 4910 E Clinton, #101, Fresno, CA 93727.

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NORTHERN CALIFORNIA: OB/GYN, FAMILY PRACTICE, PEDIATRICS. OB/GYN for busy, well established group—beautiful offices, San Francisco Bay area. Family Practitioner for group—challenging opportunity north of Lake Tahoe. Outstanding Pediatric and Dermatology practices for sale. For information about these and other practice opportunities, call/write Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (510) 376-0762.

OUR MULTISPECIALTY clinic is located within one hour of Seattle. Due to the high population growth in our service area we have opportunities for the following specialties: Family Practice, Internal Medicine, OB/GYN, Otolaryngology, and Dermatology. We offer independent practice ownership with income guarantees during start-up. Ancillary services and surgery center on campus. Good specialty mix. Well regarded for quality patient care. Please call D. M. Knight and Associates, Inc for more information and/or brochure; (206) 842-6319.

GENERAL INTERNIST in the Pacific Northwest. Busy 30 physician multispecialty group practice looking for General Internist with ICU skills and interests to join existing Internal Medicine department. Competitive salary and benefits. Send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

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ESCAPE those urban hassles and come to scenic northern California. Opportunity available to join two other Internists in private practice. Competitive salary and benefit package available. Contact Dan Jones of Gielow/Laske Associates, Inc, 306 N Milwaukee St, Milwaukee, WI 53202; FAX (414) 226-4131. Confidential inquiries welcome.

FAMILY PHYSICIAN—LEWISTON, IDAHO. Opportunity to join Family Practice group. Ambulatory and acute/inpatient care. No OB. Competitive income guarantee with opportunity to join full partnership. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501, attn: Peggy Johnson; or call (208) 743-8416.

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FAMILY PHYSICIAN—SAN FRANCISCO BAY AREA. Small Family Practice group in Alameda seeks BC/BE Family Physician to join thriving practice. No OB. Contact Peter Candell, MD, Alameda Family Physicians; (510) 769-9492.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

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OB/GYN practice in Monterey, California for sale. Solo practice grossing $600,000 annually. Fully equipped office. BE/BC principals only, please. For information write 177 Webster St, Ste A3766, Monterey, CA 93940; or call (408) 373-6245, or FAX (408) 373-2535.

COASTAL ORANGE COUNTY Family Practice, established 15 years, receipts over $550,000; desirable payor mix. Near hospitals. Call (714) 497-5975.

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AVAILABLE FOR SALE. General Surgery, hospital based practice. Colorado Springs, Colorado. 25 E Jackson, Ste 305, Colorado Springs, CO 80907; (719) 636-0075; FAX (719) 636-0070. Sale includes Penrose Hospital office lease, equipment, patient records, managed care contacts, and referral base.

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SAN DIEGO EAST COUNTY—General medical adult practice. Gross $230,000 on four days per week. Seller to retire. Low overhead, net cash flow 50% of gross. Computerized within office automated lab. Excellent personnel. 99% unadjusted collection rate. Broker—Practice Consultants; (619) 528-2321.

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FAMILY PRACTICE. Excellent opportunity to take over well established practice in growing Tri-Cities area. Hospital two blocks from office. Small town atmosphere with good recreational facilities and cultural activities, community college, and WSU branch campus. Contact G. V. Axford, MD, PO Box 2774, Pasco, WA 99302; or call (509) 547-7352, or (509) 547-4390.

SAN DIEGO, CALIFORNIA. Great opportunity to acquire solo Family Practice. Grosses $350,000 plus (three days a week). Excellent potential for expansion and growth. Computerized with in-office lab and x-ray. Excellent terms. For more information call (619) 456-6652 evenings only.

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The Bridge to China Foundation is seeking donations of books and journals for shipment to China and other disadvantaged countries in Asia. In addition to materials in medicine, the Foundation is also interested in books, journals, and magazines in any subject, which belong in a library of an institution of higher learning. They welcome material of any age. Donations are tax deductible. They request that the material be delivered to their warehouse at Pier 19 in San Francisco. Additional information about this Foundation can be obtained from its President, Jeffrey Smith, EdD, at 801 Franklin St, Oakland, CA 94607; (510) 834-3082.

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 4-6, 1992, Scottsdale.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 13-18, 1992, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-13, 1992, Copper Mountain.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1992, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 30-August 1, 1992, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 1-3, 1992, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 23-26, 1992, Sheraton Grand Torrey Pines, La Jolla, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 14-16, 1992, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): April 24, 26, 1992, Valley River Inn; November 6-8, 1992, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. September 16-19, 1992, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 9-12, 1992, Jantzen Beach, Oregon.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 11-13, 1992, Jackson Lake Lodge, Moran.

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One Of A Kind

Zantac®

ranitidine HCl/Glaxo 150 mg and 300 mg tablets

Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.

2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

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Please see Brief Summary of Prescribing Information on adjacent page.

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Of all the H_2-receptor antagonists, only Axid heals and relieves reflux esophagitis at its standard duodenal ulcer dosage. Axid, **150** mg b.i.d., relieves heartburn in **86%** of patients after one day and **93%** after one week.[1]

AXID®
nizatidine
150 mg b.i.d.

ACID TESTED. PATIENT PROVEN.

1. Data on file, Lilly Research Laboratories. *See accompanying page for prescribing information.*

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NZ-2947-B-249304

AXID®

nizatidine capsules

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: 1. *Active duodenal ulcer*—for up to 8 weeks of treatment at a dosage of 300 mg h.s. or 150 mg b.i.d. Most patients heal within 4 weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a dosage of 150 mg h.s. at bedtime. The consequences of therapy with Axid for longer than 1 year are not known.

3. *Gastroesophageal reflux disease (GERD)*—for up to 12 weeks of treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn at a dosage of 150 mg b.i.d.

Contraindication: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups.The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of anti-androgenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

PV 2093 AMP [101591]

Additional information available to the profession on request.

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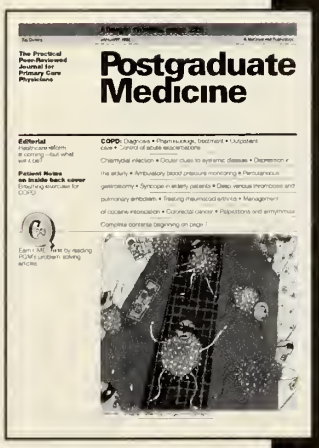

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(Hirsch CH, Winograd CH: Clinic-based primary care of frail older patients in California. West J Med 1992 Apr; 156:385-391)

We surveyed medical directors of primary care clinics in California to learn how those clinics cared for their frail older patients. Of 143 questionnaires sent, 127 (89%) were returned. A median of 30% of all patient encounters were with persons aged 65 or older, and a median of 20% of older patients were considered frail. A total of 20% of the clinics routinely provided house calls to homebound elderly patients. Of clinics involved in training medical students or physicians (teaching clinics), 70% had at least one physician with an interest in geriatrics, compared with 42% of nonteaching clinics ($P < .005$). For frail patients, 40% of the clinics routinely performed functional assessment, while 20% routinely did an interdisciplinary evaluation. Continuing education in geriatrics emerged as a significant independent correlate of both functional assessment and interdisciplinary evaluation. Among the 94 clinics with a standard appointment length for the history and physical examination, only 11 (12%) allotted more than 60 minutes for frail patients. The data suggest that certain geriatric approaches are being incorporated into clinic-based primary care in California but do not provide insight into their content or clinical effects.

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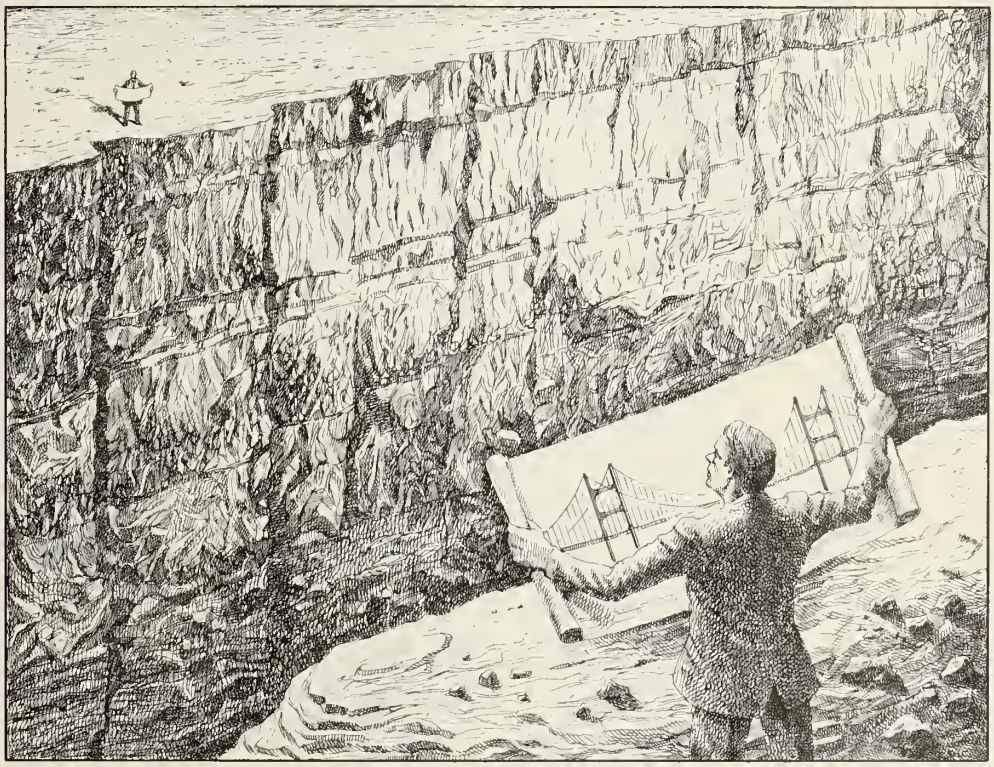

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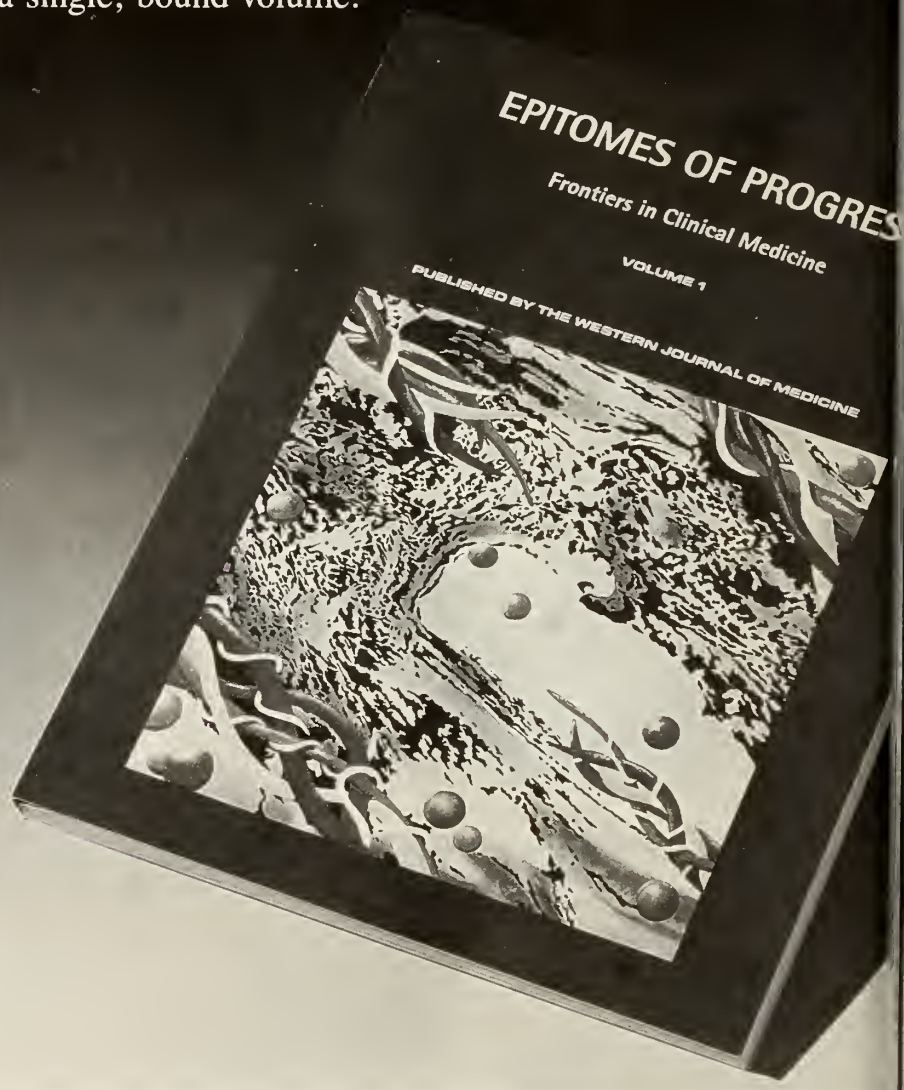

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2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
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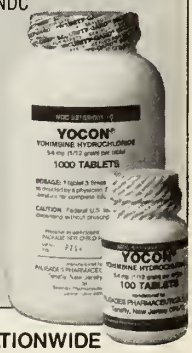

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(Lester P, Partridge JC, Cooke M: Postnatal human immunodeficiency virus antibody testing—The effects of current policy on infant care and maternal informed consent. West J Med 1992 Apr; 156:371-375)

Routine human immunodeficiency virus (HIV) antibody screening of umbilical cord blood identifies neonates at risk for HIV infection but may hold risks as well as benefits for infants and mothers. We describe the effect of testing on infant placement and care and report the women's understanding of pretest counseling and consent. In a case-control analysis of 327 tested infants, seropositive infants (13) had a higher rate of discharge to home (62%) than did controls (31%). More case infants (100%) received follow-up care and vaccinations than control infants (46%). Of 32 women interviewed after HIV antibody test informed consent, only 31% understood that a positive cord blood test result was inconclusive for the infant, and most (78%) did not identify any associated socioeconomic risks. Most (88%) stated an interest in learning their serostatus, but only 22% returned for test results. Despite the benefits of HIV antibody testing of at-risk infants, current testing and counseling procedures inadequately inform women, limiting the testing benefits to them.

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HIV COUNSELING

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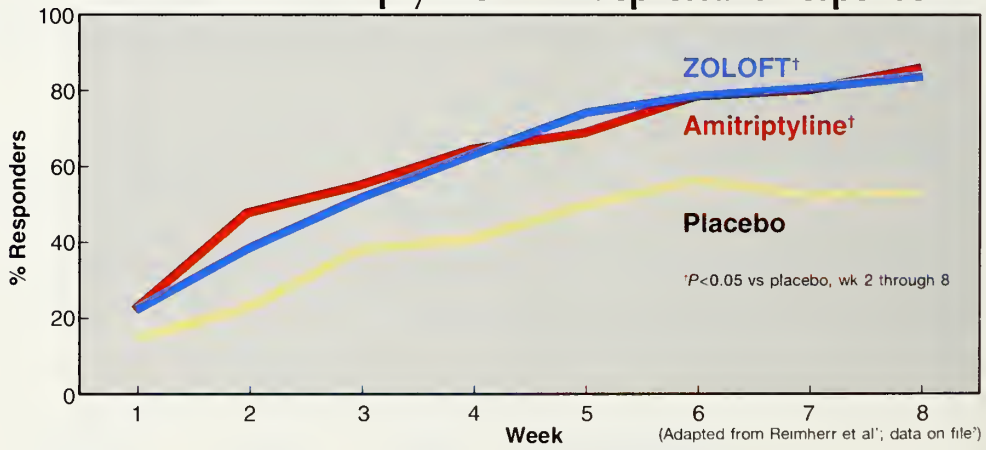
ZOLOFT...Effective in the Treatment of Depression

ZOLOFT vs Amitriptyline: Antidepressant Response*[1,2]



(Adapted from Reimherr et al[1]; data on file[2])

*Observed cases, evaluable patients (ie, patients who took drug on or after double-blind treatment day 11 and who had efficacy evaluations within that same time frame); response is defined as a CGI-Improvement score of 1 (very much improved) or 2 (much improved) at time point. Patient numbers for each regimen: ZOLOFT—wk 1=117, wk 2=120, wk 3=106, wk 4=98, wk 5=93, wk 6=94, wk 7=83, wk 8=80; amitriptyline—wk 1=116, wk 2=113, wk 3=111, wk 4=104, wk 5=102, wk 6=92, wk 7=89, wk 8=76; placebo—wk 1=124, wk 2=120, wk 3=116, wk 4=108, wk 5=97, wk 6=89, wk 7=94, wk 8=85.

Double-blind, multicenter, placebo-controlled, parallel study of antidepressant effects of ZOLOFT vs amitriptyline in 448 subjects who met DSM-III criteria for major depression. Symptoms were assessed after a single-blind, 7-day to 14-day placebo washout. Patients were randomly assigned to ZOLOFT, amitriptyline, or placebo for 8 wk. Daily dosage ranges: ZOLOFT—50-200 mg; amitriptyline—50-150 mg.

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ZOLOFT...Effective Continuation Therapy[2,3]

- Responders to ZOLOFT during an 8-week acute-treatment phase were randomized to continue on ZOLOFT or placebo
- A significantly lower relapse rate* was observed for patients treated with ZOLOFT compared with those on placebo, in an assessment of the first 8 weeks of the continuation period
- The effectiveness of ZOLOFT has not been systematically evaluated in long-term use for more than 16 weeks

ZOLOFT...Physician and Patient Confidence

- Low risk of toxicity in overdose
- ZOLOFT has a lower incidence of tricyclic-like side effects and a low incidence of nervousness, anxiety, and agitation
- The most common side effects of ZOLOFT include nausea, diarrhea or loose stools, tremor, insomnia, somnolence, and dry mouth

ZOLOFT...Once-Daily Dosing May Enhance Patient Compliance

- ZOLOFT is available in 50-mg and 100-mg scored tablets for flexible, once-daily dosing
- ZOLOFT can be taken in the morning or evening, with or without food

*Relapsing patients were those who became ill (CGI-Severity score ≥4 at any visit) during the double-blind continuation phase and who remained ill during the rest of their time in the study.

Responders in an 8-wk, open-label, acute-treatment study entered a double-blind continuation phase and were randomized to ZOLOFT or placebo. ZOLOFT daily dosage range: 50-200 mg.

References: 1. Reimherr FW, Chouinard G, Cohn CK, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. *J Clin Psychiatry.* 1990;51(12, suppl B):18-27. **2.** Data on file. Pfizer Inc, New York, NY. **3.** Doogan DP, Caillard V. Sertraline in the prevention of depression. *Br J Psychiatry.* 1992;160:217-222.

Please see brief summary of prescribing information on adjacent page.

ONCE-A-DAY

Zoloft™

(sertraline HCl) 50 mg 100 mg scored tablets

BRIEF SUMMARY

ZOLOFT™ (sertraline HCl)

INDICATIONS AND USAGE: ZOLOFT (sertraline hydrochloride) is indicated for the treatment of depression.

CONTRAINDICATIONS: None known. **WARNINGS: In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that ZOLOFT (sertraline hydrochloride) not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI.** **PRECAUTIONS** ***General:*** **Activation of Mania/Hypomania** - During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT (sertraline hydrochloride) treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants. **Weight Loss** - Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss. **Seizure** - ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. Accordingly, like other antidepressants, ZOLOFT should be introduced with care in epileptic patients. **Suicide** - The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Weak Uricosuric Effect** - ZOLOFT is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown, and there have been no reports of acute renal failure with ZOLOFT. **Use in Patients with Concomitant Illness** - Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses. ZOLOFT has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received ZOLOFT in double-blind trials were evaluated and the data indicate that ZOLOFT is not associated with the development of significant ECG abnormalities. ZOLOFT is extensively metabolized by the liver. The pharmacokinetics of ZOLOFT have not been studied in patients with significant hepatic dysfunction nor have patients with significant hepatic dysfunction been evaluated during treatment with ZOLOFT. Accordingly, ZOLOFT should be used with caution in such patients. Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until the pharmacokinetics of ZOLOFT have been studied in patients with renal impairment and until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with ZOLOFT, it should be used with caution in such patients. **Interference with Cognitive and Motor Performance** - In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. ***Information for Patients:*** Physicians are advised to discuss the following issues with patients for whom they prescribe ZOLOFT: Patients should be told that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol in depressed patients is not advised. Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast-feeding an infant. ***Laboratory Tests:*** None. ***Drug Interactions:*** **Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins** - Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT (sertraline hydrochloride) to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound ZOLOFT by other tightly bound drugs. In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either ZOLOFT (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for ZOLOFT compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the ZOLOFT group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped. **CNS Active Drugs** - In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in T_{max} for desmethyldiazepam in the ZOLOFT group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown. In a placebo-controlled trial in normal volunteers, the administration of two doses of ZOLOFT did not significantly alter steady-state lithium levels or the renal clearance of lithium. Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose. The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZOLOFT and such drugs is required. **Hypoglycemic Drugs** - In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. ZOLOFT administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown. **Atenolol** - ZOLOFT (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol. **Microsomal Enzyme Induction** - Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In clinical studies ZOLOFT was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism. **Electroconvulsive Therapy** - There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT. **Alcohol** - Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol in depressed patients is not recommended. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg in mice (10 times on a mg/kg basis and the same on a mg/m² basis as the maximum recommended human dose) and at doses up to 40 mg/kg in rats (10 times on a mg/kg basis and 2 times on a mg/m² basis, the maximum recommended human dose). There was a dose-related increase in the incidence of liver adenomas in male mice receiving sertraline at 10-40 mg/kg. No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg; this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg compared to placebo controls, this effect was not clearly drug related. Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes. A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (20 times the maximum human dose on a mg/kg basis and 4 times on a mg/m² basis). ***Pregnancy—Pregnancy Category B:*** **Teratogenic Effects** - Reproduction studies have been performed in rats and rabbits at doses up to approximately 20 times and 10 times the maximum daily human mg/kg dose (4 to 4.5 times the mg/m² dose), respectively. There was no evidence of teratogenicity at any dose level. At doses approximately 2.5-10 times the maximum daily human mg/kg dose, sertraline was associated with delayed ossification in fetuses, probably secondary to effects on the dams. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Non-teratogenic Effects** - There was also decreased neonatal survival following maternal administration of sertraline at doses as low as approximately 5 times the maximum human mg/kg dose. The decrease in pup survival was shown to be most probably due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown. **Labor and Delivery** - The effect of ZOLOFT on labor and delivery in humans is unknown. **Nursing Mothers** - It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman. **Pediatric Use** - Safety and effectiveness in children have not been established. **Geriatric Use** - Several hundred elderly patients have participated in clinical studies with ZOLOFT. The pattern of adverse reactions in the elderly was similar to that in younger patients. **ADVERSE REACTIONS** ***Commonly Observed:*** The most commonly observed adverse events associated with the use of ZOLOFT (sertraline hydrochloride) and not seen at an equivalent incidence among placebo-treated patients were: gastrointestinal complaints, including nausea, diarrhea/loose stools and dyspepsia; tremor; dizziness; insomnia; somnolence; increased sweating; dry mouth; and male sexual dysfunction (primarily ejaculatory delay). ***Associated with Discontinuation of Treatment:*** Fifteen percent of 2710 subjects who received ZOLOFT in premarketing multiple dose clinical trials discontinued treatment due to an adverse event. The more common events (reported by at least 1% of subjects) associated with discontinuation included agitation, insomnia, male sexual dysfunction (primarily ejaculatory delay), somnolence, dizziness, headache, tremor, anorexia, diarrhea/loose stools, nausea, and fatigue. ***Incidence in Controlled Clinical Trials:*** The table that follows enumerates adverse events that occurred at a frequency of 1% or more among ZOLOFT patients who participated in controlled trials comparing titrated ZOLOFT with placebo. Most patients received doses of 50 to 200 mg per day.

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials*

Adverse Experience	ZOLOFT (N=861) (Percent of Patients Reporting)	Placebo (N=853) (Percent of Patients Reporting)
Autonomic Nervous System Disorders		
Mouth Dry	16.3	9.3
Sweating Increased	8.4	2.9
Cardiovascular		
Palpitations	3.5	1.6
Chest Pain	1.0	1.6
Central and Peripheral Nervous System Disorders		
Headache	20.3	19.0
Dizziness	11.7	6.7
Tremor	10.7	2.7
Paresthesia	2.0	1.8
Hypoesthesia	1.7	0.6
Twitching	1.4	0.1
Hypertonia	1.3	0.4
Disorders of Skin and Appendages		
Rash	2.1	1.5
Gastrointestinal Disorders		
Nausea	26.1	11.8
Diarrhea/Loose Stools	17.7	9.3
Constipation	8.4	6.3
Dyspepsia	6.0	2.8
Vomiting	3.8	1.8
Flatulence	3.3	2.5
Anorexia	2.8	1.6
Abdominal Pain	2.4	2.2
Appetite Increased	1.3	0.9
General		
Fatigue	10.6	8.1
Hot Flushes	2.2	0.5
Fever	1.6	0.6
Back Pain	1.5	0.9
Metabolic and Nutritional Disorders		
Thirst	1.4	0.9
Musculoskeletal System Disorders		
Myalgia	1.7	1.5
Psychiatric Disorders		
Insomnia	16.4	8.8
Sexual Dysfunction-Male (1)	15.5	2.2
Somnolence	13.4	5.9
Agitation	5.6	4.0
Nervousness	3.4	1.9
Anxiety	2.6	1.3
Yawning	1.9	0.2
Sexual Dysfunction-Female (2)	1.7	0.2
Concentration Impaired	1.3	0.5
Reproductive		
Menstrual Disorder (2)	1.0	0.5
Respiratory System Disorders		
Rhinitis	2.0	1.5
Pharyngitis	1.2	0.9
Special Senses		
Vision Abnormal	4.2	2.1
Tinnitus	1.4	1.1
Taste Perversion	1.2	0.7
Urinary System Disorders		
Micturition Frequency	2.0	1.2
Micturition Disorder	1.4	0.5

*Events reported by at least 1% of patients treated with ZOLOFT are included.
(1) - % based on male patients only: 271 ZOLOFT (primarily ejaculatory delay) and 271 placebo patients.
(2) - % based on female patients only: 590 ZOLOFT and 582 placebo patients.

Other Events Observed During the Premarketing Evaluation of ZOLOFT (sertraline hydrochloride): During its premarketing assessment, multiple doses of ZOLOFT were administered to approximately 2700 subjects. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section. **Autonomic Nervous System Disorders**—*Infrequent:* flushing, mydriasis, increased saliva, cold clammy skin; *Rare:* pallor. **Cardiovascular**—*Infrequent:* postural dizziness, hypertension, hypotension, postural hypotension, edema, dependent edema, periorbital edema, peripheral edema, peripheral ischemia, syncope, tachycardia; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, varicose veins. **Central and Peripheral Nervous System Disorders**—*Frequent:* confusion; *Infrequent:* ataxia, abnormal coordination, abnormal gait, hyperesthesia, hyperkinesia, hypokinesia, migraine, nystagmus, vertigo; *Rare:* local anesthesia, coma, convulsions, dyskinesia, dysphonia, hyporeflexia, hypotonia, ptosis. **Disorders of Skin and Appendages**—*Infrequent:* acne, alopecia, pruritus, erythematous rash, maculopapular rash, dry skin; *Rare:* bullous eruption, dermatitis, erythema multiforme, abnormal hair texture, hypertrichosis, photosensitivity reaction, follicular rash, skin discoloration, abnormal skin odor, urticaria. **Endocrine Disorders**—*Rare:* exophthalmos, gynecomastia. **Gastrointestinal Disorders**—*Infrequent:* dysphagia, eructation; *Rare:* diverticulitis, fecal incontinence, gastritis, gastroenteritis, glossitis, gum hyperplasia, hemorrhoids, hiccup, melena, hemorrhagic peptic ulcer, proctitis, stomatitis, ulcerative stomatitis, tenesmus, tongue edema, tongue ulceration. **General**—*Frequent:* asthenia; *Infrequent:* malaise, generalized edema, rigors, weight decrease, weight increase; *Rare:* enlarged abdomen, halitosis, otitis media, ophthous stomatitis. **Hemotopoietic and Lymphatic**—*Infrequent:* lymphadenopathy, purpura; *Rare:* anemia, anterior chamber eye hemorrhage. **Metabalic and Nutritional Disorders**—*Rare:* dehydration, hypercholesterolemia, hypoglycemia. **Musculoskeletal System Disorders**—*Infrequent:* arthralgia, arthrosis, dystonia, muscle cramps, muscle weakness; *Rare:* hernia. **Psychiatric Disorders**—*Infrequent:* abnormal dreams, aggressive reaction, amnesia, apathy, delusion, depersonalization, depression, aggravated depression, emotional lability, euphoria, hallucination, neurosis, paranoid reaction, suicide ideation and attempt, teeth-grinding, abnormal thinking; *Rare:* hysteria, somnambulism, withdrawal syndrome. **Reproductive**—*Infrequent:* dysmenorrhea (2), intermenstrual bleeding (2); *Rare:* amenorrhea (2), balanoposthitis (1), breast enlargement (2), female breast pain (2), leukorrhea (2), menorrhagia (2), atrophic vaginitis (2).

(1) - % based on male subjects only: 1005; (2) - % based on female subjects only: 1705.

Respiratory System Disorders—*Infrequent:* bronchospasm, coughing, dyspnea, epistaxis; *Rare:* bradypnea, hyperventilation, sinusitis, stridor. **Special Senses**—*Infrequent:* abnormal accommodation, conjunctivitis, diplopia, earache, eye pain, xerophthalmia; *Rare:* abnormal lacrimation, photophobia, visual field defect. **Urinary System Disorders**—*Infrequent:* dysuria, face edema, nocturia, polyuria, urinary incontinence; *Rare:* oliguria, renal pain, urinary retention. **Laboratory Tests** In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation. ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance. **DRUG ABUSE AND DEPENDENCE** ***Controlled Substance Class*** - ZOLOFT (sertraline hydrochloride) is not a controlled substance. ***Physical and Psychological Dependence*** - ZOLOFT has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. However, the premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. As with any new CNS active drug, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of ZOLOFT misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior) **OVERDOSAGE** ***Human Experience*** - There have been 3 cases of ZOLOFT (sertraline hydrochloride) overdosage (approximately 750-2,100 mg). No specific therapy was required for any of the 3 patients, all of whom recovered completely. ***Management of Overdoses*** - Establish and maintain an airway, insure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. There are no specific antidotes for ZOLOFT. Due to the large volume of distribution of ZOLOFT, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

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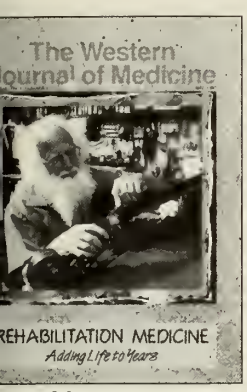

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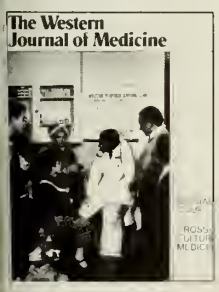

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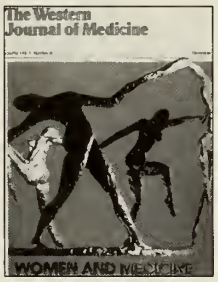

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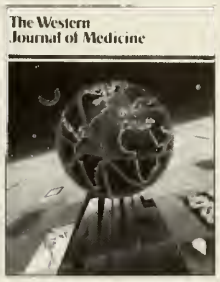

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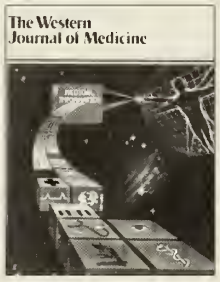

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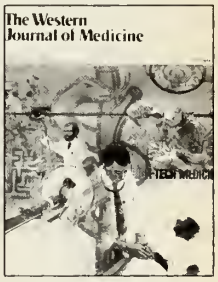

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References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade: Verapamil in Focus.* New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol.* 1990;66:131-1S1. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow-release verapamil in essential hypertension. *Eur J Clin Pharmacol.* 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation.* 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology.* 1988;39:1025-1029.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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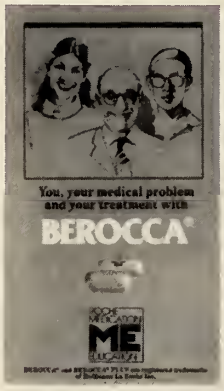

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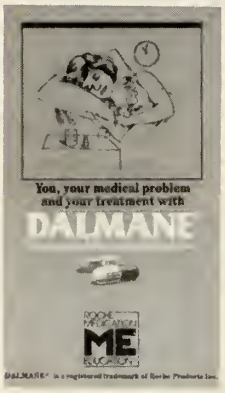

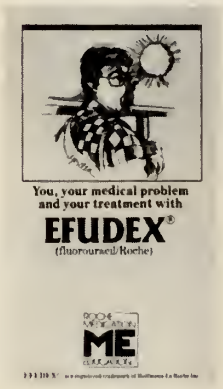

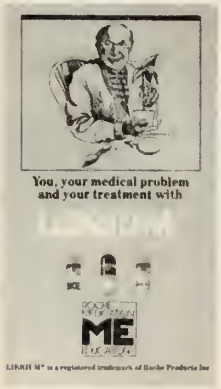

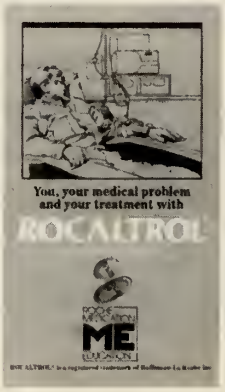

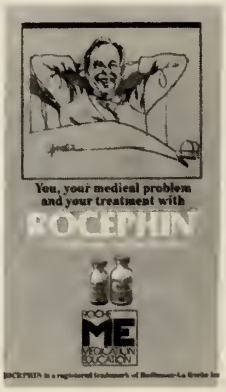

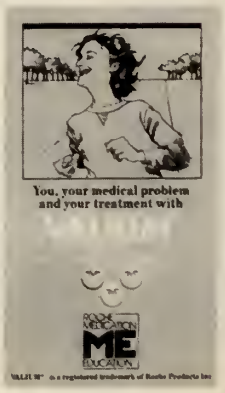

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ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal morbidity and mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation.

Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maximum daily human dose when based on mg/kg and mg/m², respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in gestation and during lactation, reduced offspring body weight was seen at ≥25 mg/kg/day, and changes in renal histology (juxtaglomerular cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Accupril® (Quinapril Hydrochloride Tablets)

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m² basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro chromosome* aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m², respectively).

Pregnancy

Pregnancy Category D: See WARNINGS, Fetal/Neonatal morbidity and mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

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* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

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The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

June 4-6—**Arizona Medical Association—Annual Meeting.** Scottsdale. Thurs-Sat. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 17-22—**Anesthesiology Review Course.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

CARDIOLOGY

April 21-23—**2nd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 1-2—**2nd International Symposium on Thrombolytic Therapy in Acute Ischemic Stroke.** Scripps Clinic and Research Foundation at San Diego Marriott, La Jolla. Fri-Sat. Contact: Scripps Clinic, Box 403C, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 26-28—**2nd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

May 30—**Regression of Coronary Artery Disease.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

August 13-15—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $325-$425. Contact: UCSF.

September 12—**Stress Echocardiography.** Sutter Health at Hyatt Regency, Sacramento. Sat. Contact: Sutter Health, (916) 733-3883.

September 25-26—**Coronary Interventions: 1992.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sat. 14 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

DERMATOLOGY

May 16-17—**Advanced Dermatologic Surgery Workshop.** UCLA at Dermatologic Surgery Center. Sat-Sun. 15 hrs. $400-$800. Contact: UCLA Extension.

July 14-18—**Dr. Hugh Greenway's Eighth Annual Conference: Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation at UCSD Campus and Scripps Clinic, La Jolla. Wed-Sat. 36 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

July 30-August 1—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 24 hrs. $425. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

August 10-12—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

May 6-10—**14th Biannual: Wound Management Workshop.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 18 hrs. $200-$435. Contact: UCSD.

May 11-15—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. Contact: UCSD.

May 31-June 3—**21st Annual Scientific Assembly.** CAL/ACEP at Westin Mission Hills Resort, Rancho Mirage. Sun-Wed. 13.5 hrs. Contact: CAL/ACEP, (800) 735-2237.

June 22-26—**Emergency Medicine Symposia III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. Contact: UCSD.

August 17-21—**Emergency Medicine Symposia II.** UCSD at Basic Science Building. Mon-Fri. Contact: UCSD.

August 19-23—**Wilderness Medicine: 1992.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $395. Contact: Gene Allred, MD, PO Box 321, Yreka 96097. (800) 888-5632.

FAMILY PRACTICE/PRIMARY CARE

May 10-15—**Family Medicine: The Foundation of Prevention, Fitness and Wellness.** Uniformed Services Academy of Family Physicians at Parc Oakland Hotel & Convention Center. Sun-Fri. Contact: USAFP, 11512 Allecingie Pkwy, Richmond, VA 23235 (804) 794-2106.

May 26-30—**Family Practice Refresher Course.** UCLA-Santa Monica Hospital Medical Center at Miramar Sheraton Hotel, Santa Monica. Tues-Sat. 32 hrs. $445. Contact: UCLA Extension.

June 15-20—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Marriott Hotel, Newport Beach. Mon-Sat. Contact: UCI.

June 18-21—**Office Gynecology: Primer for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 18 hrs. $188-$325. Contact: UCLA Extension.

July 6-9—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

August 7-9—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 21-23—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 21-23—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Loews Coronado Bay Resort, Coronado Island, San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 23-25—**7th Annual Primary Care Medicine: Principles and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 15 hrs. $485. Contact: UCSF.

(Continued on Page 366)

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(Continued from Page 364)

GERIATRICS

April-June 1992—**Health Aspects of Aging: Promoting Health and Preventing Disability.** UCLA at School of Public Health. Tuesdays. $225. Contact: UCLA.

INFECTIOUS DISEASES

April 25—**HIV Update.** UCDMC at Cancer Center Auditorium. Sat. Contact: UCD.

April 29-May 1—**13th Annual Advances in Infectious Diseases.** UCSF at San Francisco. Wed-Fri. $400. Contact: UCSF.

May 6-8—**13th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. $400. Contact: UCSF.

September 19—**AIDS.** Sutter Health at Sacramento Inn. Sat. Contact: Sutter Health, (916) 733-3883.

INTERNAL MEDICINE

May 1-4—**Molecular Biology of Hearing and Deafness.** UCSD at La Jolla Marriott. Fri-Mon. Contact: UCSD.

May 11-15—**20th Annual Advances in Internal Medicine.** UCSF at Ritz-Carlton Hotel, San Francisco. Mon-Fri. 33 hrs. $610. Contact: UCSF.

May 23-25—**California Society of Internal Medicine—Annual Meeting.** Hotel Del Coronado, San Diego. Contact: Cynthia Eaton, CSIM, (415) 882-5198.

June 22-26—**20th Annual Advances in Internal Medicine.** UCSF at Cole Hall Parnassus Campus. Mon-Fri. 32 hrs. $610. Contact: UCSF.

August 29-September 3—**10th Comprehensive Nephrology Review Course.** UCLA at Beverly Hilton Hotel, Beverly Hills. Sat-Thurs. 51 hrs. $850. Contact: UCLA Extension.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

NEUROLOGY

July 30-August 1—**New Advances in Common Neurological Disorders.** UCSD at Catamaran Hotel, San Diego. Thurs-Sat. Contact: UCSD.

OB/GYN

June 5-7—**Advanced Fetal Heart Rate Monitoring.** Memorial/UCI Center for Health Education at Radisson Hotel, Palm Springs. Fri-Sun. Contact: UCI.

July 26-29—**5th Annual In Vitro Fertilization and Embryo Transfer: A Comprehensive Update—1992.** UCLA at Four Seasons Biltmore Hotel, Santa Barbara. Sun-Wed. 20.5 hrs. $400-$522. Contact: UCLA Extension.

July 29—**10th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Wed-Sat. Contact: UCI.

OCCUPATIONAL/ENVIRONMENTAL

June 5-6—**Occupational and Environmental Medicine.** UCD. Fri-Sat. Contact: UCD.

July 26-31—**Sports Medicine.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

ONCOLOGY

April 30-May 3—**Breast Cancer Conference.** Memorial/UCI Center for Health Education at Hyatt Regency, Long Beach. Thurs-Sun. Contact: UCI.

OPHTHALMOLOGY

May 15-16—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 403C, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 10-13—**Uveitis and Retinal Frontiers.** UCSF at Carmel Valley Ranch Resort. Thurs-Sun. Contact: UCSF.

ORTHOPEDICS

June 14-19—**16th Annual Fingers to the Toes.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. Contact: UCD.

PATHOLOGY

April-May 1992—**Bay Area Seminars in Cytopathology: 1992.** UCSF at Health Sciences West on Campus. Thursdays. 10 hrs. $150. Contact: UCSF.

May 16—**Fine Needle Aspiration Basic Tutorial.** UCSF. Sat. 12 hrs. $650. Contact: UCSF.

May 21-22—**Curent Issues in Anatomic Pathology: 1992.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Fri. 13 hrs. $325. Contact: UCSF.

June 6—**Pathology Course.** Sutter Health at Buhler Building, Sacramento. Sat. Contact: Sutter Health, (916) 733-3883.

August 7-8—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD at La Jolla. Fri-Sat. 15 hrs. Contact: Daniel Gormley, MD, 412 W Carroll Dr, Ste 207, Glendora 91740. (818) 963-7684.

August 9-15—**12th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton, Mauna Lani Kohala Coast, Big Island of Hawaii. Sun-Sat. 27 hrs. $950. Contact: UCSF.

PEDIATRICS

April 24-26—**1992 West Coast Regional Conference on Pediatric Psychology.** UCSF at Union Square Holiday Inn, San Francisco. Wed-Fri. Contact: UCSF.

May 14-16—**25th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $325. Contact: UCSF.

June 26-28—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. Contact: Continuing Education, (619) 576-4072.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 366)

July 13-22—**Lactation Management Education Program.** UCSD. 1½ wks. Contact: UCSD.

July 17-August 5—**Lactation Management Education Program.** UCSD. 1½ wks. Contact: UCSD.

August 24-26—**Pediatrics Update: 1992.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

PSYCHIATRY

April 23-24—**11th Annual Conference on Child Abuse and Neglect.** UCDMC at Radisson Hotel, Sacramento. Thurs-Fri. 12 hrs. $175. Contact: UCD.

August 4-9—**Neuropsychiatric Aspects of Politics and Politicians.** American Academy of Family Physicians and Southern California Neuropsychiatric Institute at Mauna Kea Beach Hotel, Kamuela. Tues-Sun. 22.5 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

August 7-11—**The Power of the Art—Suggestive Therapeutics: An Introduction to Medical Hypnosis.** UCSD at Mission Bay Hilton, San Diego. Fri-Tues. Contact: UCSD.

PULMONARY MEDICINE

May 16—**Pulmonary Medicine.** Sutter Health at Sheraton Hotel, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

September 17-19—**11th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $410. Contact: UCSF.

RADIOLOGY

April 19-24—**Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $470. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 25—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $125. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

May 4-8—**MRI: A State of the Art Clinical Review.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Mon-Fri. 23.5 hrs. $540. Contact: UCSD.

May 8-10—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 15 hrs. $400. Contact: UCSD.

May 18-22—**Practical Body Imaging: US, CT, and MRI in the 1990s.** UCSF at Marriott's Tenaya Lodge at Yosemite. Mon-Fri. 21 hrs. $595. Contact: UCSF.

May 21-24—**Doppler and Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Thurs-Sun. 21.5 hrs. Contact: UCSD.

June 4-6—**Interventional Hepatobiliary Radiology: Percutaneous Portacaval Shunts, Biliary Stents, Tumor Chemoembolization, Lithotripsy.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17.5 hrs. $425. Contact: UCSF.

June 4-6—**Vascular Stents 1992: A Comprehensive Symposium.** Scripps Clinic and Research Foundation, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 17-19—**Vascular Imaging and Intervention for the '90s.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Fri-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-22—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Mon-Wed. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-24—**Clinical Imaging for the Non-Radiologist.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Quail Lodge, Carmel. Thurs-Sun. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 27-August 1—**Advanced Neuro MRI—Beyond Spin Echo and Musculoskeletal MRI.** Hoag Memorial Hospital Presbyterian at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Sat. 32 hrs. $645. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 10-14—**Radiology & Clinical Correlation for Non-Radiologists.** UCSD at Hotel Del Coronado, San Diego. Mon-Fri. Contact: UCSD.

SURGERY

April-May 1992—**Temporal Bone Surgical Dissection Courses.** House Ear Institute at Los Angeles. 6 days each. 53 hrs. $1100. Contact: Antonio De la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext 7079.

June 25-27—**9th Annual Meeting on Arthroscopic Surgery of the Shoulder.** UCSD and Tri-City Orthopaedic Surgery Medical Group at Hyatt Regency, La Jolla. Thurs-Sat. Contact: James Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 940-2066.

May 7-8—**Advanced Techniques in Laparoscopic Surgery for the General Surgeon.** UCD. Thurs-Fri. 15 hrs. Contact: UCD.

GENERAL/MULTIDISCIPLINARY

May 4-7—**The Best Approach 1992: Effective and Efficient Strategies in Pulmonary Medicine, Sports Medicine, Cardiology, Radiology and More.** Group Health Cooperative at Royal Waikoloan, Kohala Coast, Hawaii. Mon-Thurs. 20 hrs. $350. Contact: Group Health Cooperative, CX5, 201 16th Ave East, Seattle, WA 98112. (206) 326-3441.

June 5-7—**Medicine Meets Virtual Reality.** UCSD at La Jolla Village Inn. Fri-Sun. Contact: UCSD.

July 12-17—**21st Annual Summer School of Alcohol, Tobacco and Other Drugs.** UCSD. Sun-Fri. Contact: UCSD Extension.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

April 23-26—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

April 25—**Second Annual Women's Health Care Issues Conference.** Children's Hospital at University Hospital, Denver. Sat. Contact: Trish Beachy, (303) 270-8376.

May 4-8—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

May 8-9—**A Caring Affair.** Children's Hospital, Denver. Fri-Sat. Contact: Angela Pollack, (303) 861-6506.

June 12-13—**Fifth Annual Summer in the Mountains Conference.** Children's Hospital of Denver in Gunnison. Fri-Sat. Contact: Mary Haley, (303) 861-6946 or (800) 225-0010.

June 19-20—**Neonatal Resuscitation Course.** Children's Hospital of Denver in Laramie, Wyoming. Fri-Sat. Contact: Lois Pine, (303) 777-7166.

June 23-25—**Community Health Traineeship.** Children's Hospital, Denver. Tues-Thurs. Contact: Pat Winter, (303) 861-6668.

July 9—**Cultural Considerations in Perinatal Nursing.** Children's Hospital at University Hospital, Denver. Thurs. Contact: Trish Beachy, (303) 270-8376.

August 17-21—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

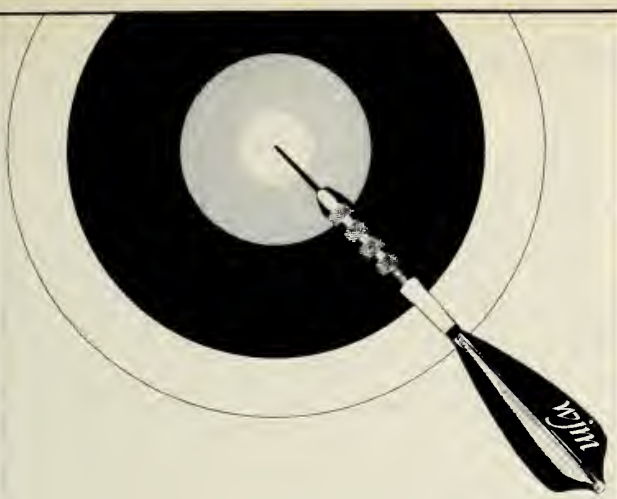
September 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

September 16-17—**Neonatal Resuscitation Hospital-Based Instructor Course.** Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

September 17, 24, October 1, 8—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Four consecutive Thursdays. Contact: Trish Beachy, (303) 270-8376.

October 23-24—**Fifteenth Annual Perinatal Conference.** Children's Hospital of Denver in Fort Collins. Fri-Sat. Contact: Sharon Adams, (303) 861-6946 or (800) 225-0010.

(Continued on Page 448)



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Indications and Usage: *1) Short-term treatment of active duodenal ulcer, (2) maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer, (3) short-term treatment of active benign gastric ulcer, (4) erosive gastroesophageal reflux disease, (5) prevention of upper gastrointestinal bleeding in critically ill patients, (6) treatment of pathological hypersecretory conditions*

Contraindications: *Tagamet is contraindicated for patients known to have hypersensitivity to the product*

Precautions: *Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of Tagamet (cimetidine hydrochloride) Injection by intravenous bolus.*

Symptomatic response to Tagamet therapy does not preclude the presence of a gastric malignancy There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy

Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

Tagamet has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole Clinically significant effects have been reported with the warfarin anticoagulants, therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when Tagamet is administered concomitantly Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects

However, a crossover study in healthy subjects receiving either Tagamet 300 mg q i.d. or 800 mg h s concomitantly with a 300 mg b i d dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h s regimen, particularly in subjects aged 54 years and older Data beyond ten days are not available (Note All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

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Pregnancy Category B Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Tagamet. There are, however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Lack of experience to date precludes recommending Tagamet for use in children under 16 unless anticipated benefits outweigh potential risks, generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache Reversible confusional states (e g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported Reversible impotence in patients with pathological hypersecretory disorders receiving Tagamet, particularly in high doses for at least 12 months, has been reported The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastia has been reported in patients treated for one month or longer Decreased white blood cell counts in Tagamet-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported As with some other H_2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia Dose-related increases in serum transaminase have been reported Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving Tagamet has been reported Small, possibly dose-related increases in plasma creatinine have been reported Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely Rare cases of polymyositis have been reported, but no causal relationship has been established Mild rash and, very rarely, cases of severe generalized skin reactions (e g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists Reversible alopecia has been reported very rarely*

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BRS-TG LB7

1. Data from randomized, controlled studies. On file, SmithKline Beecham Pharmaceuticals.

2. Palmer RH, Frank WO, Rockhold FW, et al. Cimetidine 800 mg twice daily for healing erosions and ulcers in gastroesophageal reflux disease. *J Clin Gastroenterol* 1990;12(suppl 2):S29-S34.

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Articles

Postnatal Human Immunodeficiency Virus Antibody Testing
The Effects of Current Policy on Infant Care and Maternal Informed Consent

PATRICIA LESTER, MA; JOHN COLIN PARTRIDGE, MD; *and* MOLLY COOKE, MD, *San Francisco, California*

Routine human immunodeficiency virus (HIV) antibody screening of umbilical cord blood identifies neonates at risk for HIV infection but may hold risks as well as benefits for infants and mothers. We describe the effect of testing on infant placement and care and report the women's understanding of pretest counseling and consent. In a case-control analysis of 327 tested infants, seropositive infants (13) had a higher rate of discharge to home (62%) than did controls (31%). More case infants (100%) received follow-up care and vaccinations than control infants (46%). Of 32 women interviewed after HIV antibody test informed consent, only 31% understood that a positive cord blood test result was inconclusive for the infant, and most (78%) did not identify any associated socioeconomic risks. Most (88%) stated an interest in learning their serostatus, but only 22% returned for test results. Despite the benefits of HIV antibody testing of at-risk infants, current testing and counseling procedures inadequately inform women, limiting the testing benefits to them.

(Lester P, Partridge JC, Cooke M: Postnatal human immunodeficiency virus antibody testing—The effects of current policy on infant care and maternal informed consent. West J Med 1992 Apr; 156:371-375)

Perinatally acquired human immunodeficiency virus (HIV) affects an increasing number of women and children.[1] In 1989, an estimated 6,079 infants were born to HIV-infected women in the United States.[2] Because 80% of HIV-positive women are of reproductive age, testing is occurring with increasing frequency in obstetric and neonatal settings. In 1985 the Centers for Disease Control (CDC) recommended maternal HIV antibody testing for women living in high-prevalence areas who have a significant risk of infection, including a history of transfusion, sexual risk factors, and intravenous drug use.[3] Although targeted HIV testing based on epidemiologic research may represent the most practical use of the limited resources available for testing, some groups have called for an HIV screening policy for all pregnant women and newborns.[4-6] Most health care professionals believe that a knowledge of maternal serostatus may enhance perinatal health care through appropriate HIV prevention counseling, therapeutic abortions, access to continuity of care focused on HIV-related illnesses, and early prophylactic and therapeutic interventions for women and their infants.[7,8] Since 1987, San Francisco General Hospital Medical Center has used a policy of targeted, voluntary HIV antibody testing of at-risk pregnant and postpartum women in this high-prevalence population.

While the CDC's policy primarily targets pregnant women with HIV risk factors, a substantial number of urban pregnant women at risk for HIV infection receive little or no prenatal care, precluding serostatus determination before they give birth. Consequently, the first opportunity to screen these women may be at delivery or in the immediate postnatal period. The benefits of postpartum HIV-antibody screening include early zidovudine therapy and *Pneumocystis carinii* pneumonia prophylaxis for the women and early disease detection and treatment in their infants. Postpartum screening, however, raises concerns that have been articulated about HIV testing in other populations—loss of housing, employment, and insurance and compromised medical care access, child care, and family support (S. Katz, "Driving the Sick Underground: HIV Testing—A Phony Cure," *The Nation*, May 28, 1990, pp 738-742)[9,10]—but in a group particularly at risk for discrimination due to race and poverty. Compounding these factors, a positive maternal or neonatal HIV-antibody test provides inconclusive information about the infant's long-range condition; indeed, only 25% to 35% of these newborns remain seropositive at 15 months of age.[11,12] The risks remain unexplored and unquantified, yet the arguments for testing have become more vehement with the rising HIV seroprevalence in women of childbearing age and the demonstrated benefits of early HIV therapy and prophylaxis.[13]

Practitioners of perinatal care are familiar with the difficult balance among their own values, a woman's rights, public health interests, and infants' well-being and rights.[14,15] In California, the legal requirement for informed consent for the cord blood HIV-antibody test has brought conflicts among these parties into the open. Just as for other newborn procedures, the clinician must consider the parent as a proxy for the infant. The woman, in turn, must weigh the test's risks and benefits for both herself and her newborn. Her decision is based on her understanding of complex medical and social issues and of the testing procedure and results.

To assess the actual consequences of the current HIV-antibody counseling and testing in the newborn nursery, we studied two aspects of HIV-antibody screening. Infants identified as seropositive over a two-year period were compared with seronegative control infants matched for race, mater-

From the Department of Pediatrics (Dr Partridge) and the Medicine Service (Dr Cooke), San Francisco General Hospital Medical Center, and the School of Medicine (Ms Lester), University of California, San Francisco.

Supported in part by the Bay Area Perinatal AIDS Center, San Francisco General Hospital, University of California, San Francisco, NIH Grant #HD 24640, and by a grant from the San Francisco Foundation to the University of California, San Francisco.

Reprint requests to John Colin Partridge, MD, Department of Pediatrics, Rm 6E9, 1001 Potrero Ave, San Francisco, CA 94110.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
BAPAC = Bay Area Perinatal AIDS Center
CDC = Centers for Disease Control
HIV = human immunodeficiency virus

nal risk factors, and maternal age to determine whether a positive cord blood test affects an infant's disposition and subsequent medical care. We also used an open-ended questionnaire to evaluate women's understanding of clinicians' informed consent counseling and risk and benefit disclosure for HIV-antibody testing. This questionnaire evaluated the women's understanding of the test's significance, their ability to recall disclosed benefits and risks, their motivations for consenting to the test, and their intentions to return for results. In addition, we documented whether the study group women actually returned for the follow-up appointment for after-test counseling and results. An assessment of the effects of a positive HIV test on the health care, psychosocial factors, and economic status of the women is the subject of a third study currently under way.

Population and Methods

Background—Seroprevalence Study

Beginning in 1988, routine care of recently delivered women (n = 3,753) included a standardized risk assessment to identify those at risk for HIV infection. At least one medical or social risk factor for HIV infection was identified in 345 women after delivery. Due to oversight or practical constraints, 38 women were not approached before discharge from the hospital; however, these women did not differ significantly from the study women with respect to demographics or risk factors. The remaining 307 were approached by nursery staff or their attending physicians for written informed consent for cord blood serologic testing; 279 (91%) agreed to the test, and 269 were actually tested. Of those, 13 (5%) had positive HIV-antibody cord blood tests.

Our nursery's HIV-antibody informed consent protocol specified that the women would be provided with information about the test's purpose, its risks and benefits, and the significance of a negative or positive result for a woman and her infant. The clinician described alternatives and emphasized the voluntary nature of the test. A follow-up clinic appointment for the woman was made, and she was given a slip with the time, day, and location where she should return for results and counseling. All research procedures were approved by the University of California at San Francisco Committee for Human Research.

Effects of Postnatal HIV-Antibody Testing on Infant Disposition and Care

The 13 newborns defined as case infants had a positive enzyme-linked immunosorbent assay test using cord blood that was confirmed by Western blot. Maternal race distribution included nine African Americans, three whites, and one Hispanic. Maternal age ranged from 24 to 40 years. Of the 13 infants, 10 showed signs of neonatal drug withdrawal; 8 were either premature or small for gestational age. Two died before age 15 months, one of HIV-related illness. Three infants are now symptomatic with HIV-related illnesses. Of the 13 cases, 7 have seroreverted, and 1 infant has an indeterminate serostatus.

Control infants were retrospectively selected from the 256 infants with negative cord blood tests during the same study period. They were matched for maternal race, age, and five social risk factors: drug use, history of child neglect or abuse, psychiatric history, homelessness, and other risk factors such as incarceration. Of 13 control infants, 10 experienced neonatal drug withdrawal; 6 were either premature or small for gestational age. With the exception of a gastrointestinal operation in one case infant, the case and control groups required only routine neonatal care. Table 1 compares mean birth weights, gestational ages, and Apgar scores of case and control infants. Although case infants tended to have smaller birth weights and lower gestational ages, this difference was not statistically significant given the sizes of the two groups.

TABLE 1.—*Birth Weight, Gestational Age, and Apgar Scores for Case and Control Infants*

Measurement	Infants: Case x ± SD	Infants: Control x ± SD	P
Birth weight, grams...	2,320.8 ± 744.3	2,770.0 ± 533.0	> .05
Gestational age, wk...	36.1 ± 2.98	38.4 ± 2.77	> .05
Apgar test score			
1 Min.....	7.3 ± 2.02	7.4 ± 1.32	> .1
5 Min.....	8.6 ± 0.75	8.7 ± 0.48	> .1

To evaluate the effects of a positive HIV-antibody test on the infant, we measured the proportion of control and case infants discharged to three possible locations: home, extended family, or foster care. In addition, we evaluated follow-up health care after discharge by comparing the frequency of vaccinations and continuity of care in the two groups.

Women's Comprehension of Informed Consent and Test Counseling

During two months of 1990, 33 women identified as having HIV risk factors and who consented to HIV testing were interviewed. These women were referred to one of the study investigators (J. C. P. or P. L.) after consenting to HIV testing and before cord blood test results were returned. Of these, 32 agreed to participate as interview research subjects. Of the 32 women interviewed, 7 had undergone prenatal screening and were shown to be HIV-negative; they were retested at delivery to address the possibility that the initial negative test reflected a recent infection. The racial demographics and socioeconomic status of the interviewed mothers reflected the distribution of the entire study population.

Women were asked to participate in the study within 48 hours of counseling and informed consent for cord blood testing. The interview was designed to evaluate the critical components of information transfer (Table 2); open-ended questions were asked in a neutral, nonleading fashion to prevent systematic response bias. All responses were recorded and then assigned to content categories. When women provided more than one answer for a given question, all responses were recorded. Interview responses have been reported as percentages of total answers to that question. Attendance or nonattendance of subjects at a scheduled outpatient counseling appointment after testing was documented.

TABLE 2.—*Interview to Assess Maternal Understanding of HIV-Antibody Test Informed Consent*

What was the purpose of the cord blood test?
Why did you agree to have the test done?
What were the test's risks and benefits for you and your baby?
What would a positive and negative test mean for both you and your infant?
Did hearing or thinking about the test upset or worry you at all?
Do you intend to come back to find out the test results? Why or why not?

HIV = human immunodeficiency virus

Results

Effects of Seropositivity on Newborn Disposition and Care

Seropositive newborns were discharged to their parents more frequently than their seronegative counterparts were. Of the 13 HIV-positive infants discharged from the nursery between 1988 and 1990, 8 (62%) went home with a parent, 2 to extended family, and 3 to foster care. Of the matched control infants, four (12%) were discharged to parents, six to extended family, and three to foster care. Because the number of case and control infants was small, the difference in the rate of discharge home with parents was not statistically significant ($P = .12$).

The seropositive infants received more complete follow-up care than did the control infants. All case infants received appropriate follow-up care and vaccinations, in contrast to only 6 (46%) of 13 control infants ($P < .01$). Of the 13 case infants, 9 were observed by the Bay Area Perinatal AIDS [acquired immunodeficiency syndrome] Center (BAPAC), a treatment and research group established for children and their families who are at risk for HIV infection, 1 was placed in a foster care program for infants with special medical needs, and the remaining 3 were cared for by private physicians.

Maternal Comprehension of Test Purpose and Result Significance

Most women understood that they had given permission for an HIV-antibody test but did not understand its clinical implications. Of the 32 women, 2 (6%) could not recall the purpose of the cord blood test. Only 6 (19%) thought that the HIV test evaluated their own serostatus; 13 (41%) thought that the test was only for the infant, and 11 (34%) thought it reflected the status of both mother and infant.

Most of the women appeared to understand the general concept of vertical transmission; however, 13 (41%) cited reasons other than "wanting to know if I have AIDS/HIV or the baby has AIDS/HIV" as the reason they consented to testing. These additional motivations for consenting to the test ranged from acquiescence to the physician's or a parent's authority (16%) ("the doctor/my mom wanted me to") to confirmation of negative prenatal tests (22%).

Confusion about the implications of a positive test result for both the woman and her baby was prevalent. Of the 32 women, 22 (69%) viewed a positive result as an indication that the mother was either infected with HIV or had AIDS. Eleven mothers (34%) thought that a positive test meant the baby had AIDS, and another five (16%) said the baby would be infected with HIV. Only 10 women (31%) knew that a positive test only indicates a risk factor for infection in the baby and that the baby would require later testing. Further, 6 of the 9 women (67%) counseled by an attending physician understood the test's medical meaning, but only 4 of the 23 women (17%) counseled by house staff did so.

Despite the disclosure of risks (such as lack of confidentiality and loss of housing, insurance, and work), which is a component of the informed consent protocol, these women recalled few risks associated with the test for either themselves or their infants (Table 3). Of the nine women counseled by the attending physician, six (67%) could identify at least one risk, compared with only one (4%) of those counseled by house staff. In keeping with previous studies on informed consent in other settings, our population had a better understanding of test benefits than of risks.[16,17]

TABLE 3.—*Maternal Understanding of HIV-Antibody Test Risks and Benefits*

Maternal Response	*Personal, n = 32 (%)*	*Infant, n = 32 (%)*
Risks		
None	25 (78)	28 (88)
1 or more	7 (22)	4 (12)
Stress or other's knowledge	5 (16)	0 (0)
Socioeconomic	1 (3)	0 (0)
Unclear	3 (9)	4 (12)
Benefits		
None	8 (25)	8 (25)
1 or more	24 (75)	24 (75)
Early treatment	18 (56)	18 (56)
"Just knowing"	10 (31)	10 (31)
Other	1 (3)	1 (3)

HIV = human immunodeficiency virus

The women's responses to the HIV cord blood test were varied. Most thought that having an HIV test was not stressful, and most stated an interest in knowing their own serostatus. In all, 19 study subjects (59%) reported no stress and 10 (31%) indicated only mild stress when discussing the test or waiting for results. Only three women (9%) reported moderate to high stress related to the cord blood test. Most women (28; 88%) said they intended to come back for the results. Only three women (9%) indicated that they would not return because they felt certain the test would be negative, and one woman said that she just did not want to know the result. Despite the frequency of a stated desire to know the test results, only seven women (22%) returned for scheduled appointments in the hospital clinic to obtain these results.

Discussion

In this study population, a determination of HIV seropositivity was associated with a higher rate of discharge home with parents and better medical care for infants. Confusion about the meaning of a positive test result and the low return rate to learn test results, however, may limit the effects of testing as a means of improving health care and preventing HIV transmission. Special care must be taken to verify that the counseling and testing procedures maximize benefits for both women and their infants.[18]

Perinatal HIV-Antibody Testing— What Does It Mean for the Newborn?

Testing for the HIV antibody in the nursery is best undertaken in the context of a comprehensive, multidisciplinary

treatment and counseling program for both the infants and their mothers.[19,20] Although many health care institutions have developed HIV testing policies designed to meet these goals, testing programs vary widely among hospitals. The successful follow-up seen in this group indicates the possible benefits of targeted HIV testing in a model perinatal care program. In our study population, most case infants and their families became enrolled in HIV research and treatment programs through BAPAC. Because the women and infants were observed as pairs, BAPAC was able to provide psychological, medical, and social services aimed at meeting the needs of both the women and their infants. BAPAC provided follow-up of women who did not return for test results, as well as reimbursing them for child care and transportation expenses, a virtual necessity in this population. Further, BAPAC undoubtedly accounted for the high rate of discharge home with parents in this study population. This outcome contrasts markedly with experience from high-prevalence urban areas where HIV-risk infants have been abandoned in large public hospitals.[21]

Informed Consent and Pretest Counseling—How Much Does the Woman Understand?

Our study indicates that current informed consent procedures do not ensure that a woman understands the test's medical implications or socioeconomic risks. In any setting, ethical informed consent requires that a competent person select or reject a recommended procedure or treatment after understanding all reasonable risks associated with that therapy and alternative procedures. Informed consent for newborn care is complicated, however, requiring a proxy decision maker, usually one or both parents. Conflict may arise when an infant's physicians, the parent, and, in some instances, the state disagree about what is best for the newborn. The situation is further complicated in the case of HIV cord blood testing because the test, ostensibly an evaluation of the infant's blood, actually provides information about the woman's HIV status.

As long as seropositivity generates a highly charged social response, a woman's individual circumstances may reasonably warrant an estimation of risk that outweighs the current medical benefits of the HIV-antibody test,[18] and our current refusal rate of 9% for cord blood testing may be an understandable, if not optimal, result. With the future promise of earlier intervention and a broadened spectrum of antiretroviral agents, the precarious balance of rights between the proxy-mother and her infant may increasingly favor testing.

In addition to these structural issues, our results raise concerns about the process of HIV counseling and testing. Why were these women unable to reiterate the meaning of HIV cord blood testing? There are several possibilities. First, postpartum pain, analgesia, and other clinical factors may profoundly compromise information transfer during the postpartum hospital stay. Second, the physicians' effectiveness in communicating may be less than optimal. Postnatal HIV testing may be especially problematic when conducted by the infant's physician because the pediatrician is focused primarily on the infant's medical needs and may not accurately assess its mother's understanding. The HIV cord blood test is relatively difficult to comprehend, and the concept of maternal antibodies implying the possibility of infection in the newborn is abstract. It is notable, however, that the women counseled by the attending physician were consistently more able to accurately identify the test's medical meaning and socioeconomic risks than were those counseled by the house staff.

The simplest explanation for these women's decisions to accept testing without fully understanding the test's implications may be that they had little to lose. The women positive for the HIV antibody are largely women of color who are unemployed and on Medicaid; they have been referred for testing because of a history of injecting drugs, physical abuse, psychiatric problems, homelessness, or a partner's risk behavior. A positive test result cannot remove financial and social advantages that were never present. Less visible forms of discrimination, especially by family and friends, are more difficult to measure, yet they may have a much greater effect on the fabric of these women's lives. In our study and others, the women expressed concern primarily about the repercussions of a positive test result on their relationships—anger or alienation from their partners, parents, or other family members.[22]

The observation that 78% of those tested did not return to learn their test results is evidence of a failure of the current counseling and testing system to engage women at high risk for HIV infection in a comprehensive HIV prevention and care plan. Certainly this result could imply that the women, after deliberation, chose not to learn of their results in an effort to avoid the psychological or social consequences of known seropositivity. Most of them, however, indicated that they perceived few or no risks associated with the HIV-antibody test, suggesting that other factors played a role in their failure to return for test results. Maternal understanding could be improved by several strategies, such as improved house staff training in informed consent and HIV counseling, HIV counseling conducted by nonphysician counselors, and aggressive follow-up of all women tested to provide posttest counseling. Another opportunity for improved follow-up counseling is prompt availability of results, enabling serostatus determination and counseling to occur before a woman's discharge.[23] Test counseling will also be more straightforward when a diagnostic test capable of determining a newborn's viral status becomes widely available.[24,25]

Perinatal HIV-Antibody Testing Policy—Unanswered Questions

Although most public and private health organizations agree that testing, counseling, and treatment programs should be offered to pregnant and postpartum women, questions remain about the appropriate type of testing for these women. Some groups have suggested routine perinatal HIV screening programs on the grounds that targeted testing is discriminatory.[4] False-positive results in such a large, low-prevalence population would be costly, however, absorbing funding that could be used in more effective ways. Future introductions of improved infant HIV treatment or cures may mandate a routine approach to HIV-antibody screening for both pregnant and postpartum women.

Offering voluntary HIV-antibody testing of women and children at risk through written informed consent remains the most ethical and practical method for testing.[5] Knowledge of the mother's and infant's serostatus is important in providing optimal care and social support for a family. This information should not, however, be obtained against a woman's wishes or without her understanding.

Our results raise many questions about the ethics of the current informed consent procedures for HIV antibody testing: Why do women fail to understand the test's meaning and risks after giving written informed consent? What kinds of intervention might improve the outcomes? What are the psychological, social, and economic effects of a positive test result on a woman? Will seropositive infants suffer adverse consequences when their families or health care professionals learn of their serostatus? Before advocating and financing more screening, we need to define and implement procedures that meet the policy's goals.

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Articles

Cervical Cancer Incidence and Mortality in New Mexico's Hispanics, American Indians, and Non-Hispanic Whites

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High rates of cervical cancer were reported in New Mexico in the early 1970s, with especially high rates for minority women. We examined data collected from 1970 to 1987 for invasive cervical cancer and cervical carcinoma in situ for New Mexico's Hispanic, American Indian, and non-Hispanic white women to determine whether changes had occurred in cervical cancer rates since earlier reports. To further characterize the epidemiology of cervical cancer in New Mexico, we reviewed state vital statistics for cervical cancer deaths occurring between 1958 and 1987. From 1970 to 1987, the incidence for invasive cervical cancer among Hispanic (18.9 per 100,000 person-years) and American Indian women (22.0 per 100,000 person-years) was about double that for non-Hispanic white women (10.3 per 100,000). The incidence in each ethnic group decreased over time for both invasive cancer and carcinoma in situ when the data were examined by 2 time periods (1970 to 1978 and 1979 to 1987). These decreases were most dramatic for invasive cervical cancer. Cervical cancer-related death rates for Hispanics and non-Hispanic whites also decreased from 1958 to 1987. Although our data reflect declines in cervical cancer rates during the study period, further rate decreases, especially for minority women, remain an important public health goal in New Mexico.

(Becker TM, Wheeler CM, Key CR, Samet JM: Cervical cancer incidence and mortality in New Mexico's Hispanics, American Indians, and non-Hispanic whites. West J Med 1992 Apr; 156:376-379)

Cancer incidence and mortality vary markedly for many sites among the racial and ethnic groups living in the southwestern United States.[1,2] New Mexico's Hispanics, American Indians, and non-Hispanic whites—the three major racial and ethnic groups in the state—have substantial differences in rates for one site, cervical cancers.[1,3] Reviewing data collected from 1966 to 1975, Jordan and Key found strong differences in age-adjusted rates and in age-specific patterns for cervical cancer among these three ethnic groups in New Mexico, with the highest rates in American Indians, intermediate rates in Hispanics, and the lowest rates in non-Hispanic whites.[3] Cervical cytologic data collected during this period also reflected high rates of invasive and in situ cervical cancers among the minority women of the state.[1,3]

To investigate changes in cervical cancer occurrence in New Mexico that have taken place since these earlier reports, we examined data collected by the New Mexico Tumor Registry for the cervical cancer incidence from 1970 to 1987. During this period, state public health agencies and the Indian Health Service promoted cytologic screening for the early detection of cervical cancer. To assess temporal changes in the rates, we analyzed the registry data for two time periods, 1970 to 1978 and 1979 to 1987, for both invasive and in situ cancers. We also examined state vital records collected from 1958 to 1987.

Methods

The population-based New Mexico Tumor Registry, a member of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, has recorded the incidence of cancer in New Mexico since 1969.[1] Methods have been described in detail elsewhere.[1] Cases are ascertained through an active review of medical records including hospital charts, outpatient clinic records, pathology and autopsy reports, and radiation therapy records. Staff members routinely review New Mexico Bureau of Vital Statistics records for death certificates that mention cancer.

The Bureau of Vital Statistics for the state of New Mexico has determined ethnicity of decedents. Both the Bureau of Vital Statistics and the New Mexico Tumor Registry use multiple sources of information to determine ethnicity. Hispanics are identified by designation in medical records, on the basis of surname, and from statements on death certificates. American Indians are identified by statements in medical records, by place of residence, and through Indian Health Service records. Persons designated as white or Caucasian who do not have a Spanish surname are coded as non-Hispanic white. We validated the bureau's coding of Hispanic and non-Hispanic white ethnicity from data obtained from a recent case-control study of lung cancer in New Mexico, as previously described.[4]

Denominators for the incidence and mortality rates were derived from US Census Bureau estimates of the New Mexico population.[4-8] For numerators of the rates, we used the registry's surveillance system to identify all cases of in situ and invasive cervical cancers diagnosed among New Mexico residents during the period 1970 to 1987. Because of the small number of cases in other ethnic-racial groups, this

From the New Mexico Tumor Registry, University of New Mexico School of Medicine, Albuquerque.
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investigation was limited to American Indians, Hispanics, and non-Hispanic whites. Average annual age-specific and age-adjusted incidence was standardized to the 1970 US standard million population by the direct method.[1]

We also examined state death certificates collected from 1958 to 1987 on cervical cancer-related deaths—International Classification of Diseases code numbers 180.0 to 180.9—by five-year time periods and by ethnic group. We calculated age-adjusted mortality using the 1970 US population. For reference, nationwide age-adjusted cervical cancer mortality for whites and African Americans was calculated from National Center for Health Statistics data for the years 1960, 1965, 1970, 1975, and 1980.[9-13]*

Results

The age-adjusted rate of invasive cervical cancer from 1970 to 1987 in Hispanics (18.9 per 100,000 person-years) was almost double that in non-Hispanic whites. Age-specific data for 1970 to 1987 showed that American Indians and Hispanics had the highest rates of invasive cervical cancer (Figure 1).

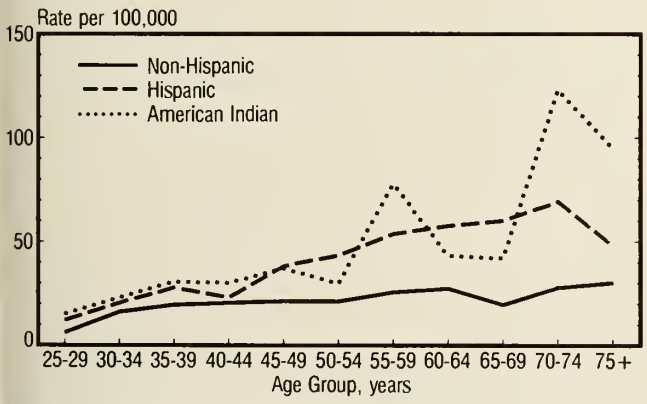

Figure 1.—Cervical cancer incidence by age and ethnic group in New Mexico are shown for invasive carcinomas, 1970 to 1987 (rates per 100,000 person-years).

Decreasing age-adjusted incidence for invasive cervical cancer is apparent for each group from a comparison of the data for the periods 1970 to 1978 and 1979 to 1987. The greatest decrease (38%) occurred among Hispanic women (Table 1).

TABLE 1.—*Age-Adjusted Incidence (Per 100,000 Person-Years) for Cervical Cancer by Ethnic Group, New Mexico, 1970 to 1978 and 1979 to 1987**

	Cervical Cancer			
	Invasive		Carcinoma In Situ	
Ethnic Group	1970-1978	1979-1987	1970-1978	1979-1987
Hispanic	23.9	14.8	37.2	34.3
American Indian	25.9	19.1	54.2	37.0
Non-Hispanic white	12.8	8.4	39.1	38.4

*From the New Mexico Tumor Registry.

The age-adjusted rate of cervical carcinoma in situ in American Indian women (44.2 per 100,000 person-years) was higher than that in non-Hispanic white (38.7) and Hispanic women (35.6) over the entire study period. Comparable age-specific patterns of carcinoma in situ were apparent in each ethnic group and across most age groups, with the highest rates occurring among women aged 25 to 34 years (Figure 2). Among women aged 65 years or older, cervical carcinoma in situ rates were highest in American Indians.

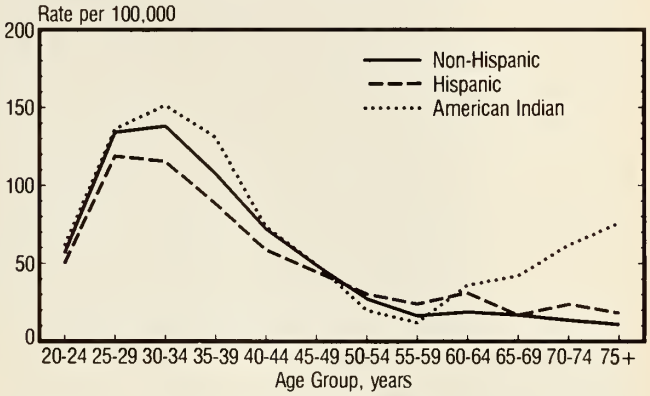

Figure 2.—Cervical cancer incidence by age and ethnic group in New Mexico is shown for in situ carcinomas, 1970 to 1987 (per 100,000 person-years).

Age-adjusted rates of cervical carcinoma in situ from 1979 to 1987 were only slightly lower than rates in 1970 to 1978 for Hispanics and non-Hispanic whites, but American Indian women showed a 32% decrease in rates (Table 1).

Mortality from cervical cancer in New Mexico declined from 1958 to 1987 (Table 2). Mortality for non-Hispanic whites was comparable with that for US whites; mortality for Hispanics and American Indians exceeded that for New Mexico's non-Hispanic whites but was consistently lower than cervical cancer mortality for US African Americans (Table 2).

Discussion

Although declining in occurrence, invasive cervical cancer in New Mexico remains more common in Hispanics and American Indians than in non-Hispanic whites. Invasive cervical cancer rates among American Indian women in this state remain among the highest reported for cervical cancer for any ethnic or racial group in the United States.[14] The high incidence and mortality for cervical cancer documented during the 1950s and 1960s[15] have been shown in recent reports to be still elevated among American Indians and Alaska Natives in other states. In western Washington, the incidence for invasive cervical cancer among American Indian women from 1974 to 1983 was high compared with that among the area's whites (standardized incidence ratio, 1.6).[16] Cervical cancer mortality among Alaska Natives exceeded that of US whites from 1969 to 1983, with standardized mortality ratios ranging from 2.1 in Eskimos to 4.0 in Aleuts.[17] In addition, cervical cancer mortality among the Seneca of New York from 1955 to 1984 and North Carolina's American Indians from 1968 to 1982 doubled the death rates for comparison populations in the respective states.[18,19] Risk factors for cervical cancer have not been characterized in American Indian women in analytic epidemiologic studies.

Hispanic women in New Mexico had almost twice the rate of invasive cervical cancer as that of non-Hispanic white women in the state. This high rate is consistent with reports for Hispanic women from other locations in the US[20,21] and in Latin America.[22,23] So far, no unifying hypothesis has emerged that can explain the consistently high rates of invasive cervical cancer in diverse groups of Hispanic women in

*Charles L. Wiggins, MSPH, provided computer programs and assisted with graphics.

TABLE 2.—*Cervical Cancer-Related Mortality Among New Mexico's Hispanics, American Indians, and Non-Hispanic Whites, 1958 to 1987**†

Ethnic Group	Time Period‡ 1958-1962	1963-1967	1968-1972	1973-1977	1978-1982	1983-1987
NM Hispanic	10.6 (66)	9.8 (65)	8.1 (56)	7.6 (56)	4.4 (38)	3.9 (39)
NM American Indian	3.8 (4)	9.8 (11)	7.8 (9)	5.9 (8)	7.7 (11)	4.8 (9)
NM non-Hispanic white	7.0 (86)	5.0 (73)	4.5 (67)	4.0 (69)	2.2 (45)	1.8 (40)
US white	8.1	7.0	5.2	4.0	3.1	2.7
US African American	19.9	18.0	14.0	11.4	9.0	7.3

NM = New Mexico, US = United States

*Age-adjusted rates per 100,000 person-years.
†From the New Mexico Bureau of Vital Statistics.
‡The numbers in parentheses indicate the number of deaths over the 5-year period.

North, Central, and South America. In studies of cervical cancer among US Hispanics, early age at first intercourse, lower socioeconomic status, and a higher number of sex partners have been linked to a higher cervical cancer incidence.[20] Studies of cervical cancer in Hispanics living outside the US have suggested additional dietary, behavioral, reproductive, or infectious disease risk factors for acquiring cervical malignancy.[22,24-27]

Mortality for cervical cancer declined substantially in New Mexico from 1958 to 1987 for Hispanic and non-Hispanic white women, consistent with decreases in cervical cancer mortality nationwide among African Americans and whites (Table 2). Nonetheless, despite the decrease, Hispanic women had almost twice the cervical cancer mortality as non-Hispanic white women throughout the study period. We lack data to determine if these ethnic differences in mortality are due to differences in cervical cancer screening or to other factors. Furthermore, we lack the necessary information to determine if the declines in cervical cancer mortality in these ethnic groups (as is observed nationwide) are a result of changes in cervical cancer screening. Temporal changes in cervical cancer mortality were not consistent for American Indian women (Table 2); the small number of cervical cancer deaths for American Indian women caused rates to fluctuate when examined by five-year time periods. Cancer mortality reflects cancer incidence in addition to survival. Previous research from the New Mexico Tumor Registry indicates poorer survival from cervical cancer among American Indians than among non-Hispanic whites in this state[28]: 52% of American Indian women survived five years after diagnosis, whereas 63% of Hispanics and non-Hispanic whites survived five years after the diagnosis of cervical cancer. For both Hispanic and American Indian women, larger proportions of cervical cancer cases were diagnosed with regional or distant disease compared with non-Hispanic white women, and larger proportions of Hispanic and American Indian women did not receive treatment of cervical cancer compared with non-Hispanic whites.[28] Thus, the survival data for cervical cancer patients in New Mexico suggest that inadequate care and a delay of treatment among minority women may contribute to the higher mortality from cervical cancer than in the non-Hispanic majority.

Possible sources of bias in the data bases used in this analysis have been previously discussed.[4,29] In addition, about 15% of deaths from cervical cancer are misclassified to the uterus as the primary site.[30] Furthermore, we have shown that disproportionate numbers of all deaths of minority people in this state are attributed to "symptoms, signs, and ill-defined conditions,"[31] and it is reasonable to assume an unknown percentage of all cervical cancer deaths is assigned to this category. Finally, another possible source of bias lies in the absence of data on hysterectomy in New Mexico's Hispanic, American Indian, and non-Hispanic white women.

Data are not yet available to explain the high cervical cancer incidence in New Mexico's Hispanic and American Indian women. Ongoing research in New Mexico has not yet shown striking risk profiles for cervical disease among local minority women. In a recent pilot study of factors causing cervical dysplasia in American Indian women (n = 100), those with dysplasia actually had fewer lifetime sex partners and fewer episodes of sexually transmitted diseases than control women with normal Papanicolaou smears.[32] Human papillomavirus (HPV) infection has also been investigated in association with Papanicolaou smear abnormalities. In a prevalence survey of cervical HPV infection in New Mexico, non-Hispanic whites had a higher prevalence of cervical HPV (13%) compared with Hispanic (9.7%) and American Indian women (6.6%).[33] This pattern is inconsistent with the expected pattern of the prevalence of HPV if HPV were carcinogenic.[34] Nonetheless, a large proportion of the New Mexico women with cervical HPV infection had HPV types that are more strongly associated with cervical cancer.[35]

The descriptive data that we have presented show that minority women in New Mexico remain at high risk for cervical cancer; unfortunately, we are lacking information on risk factors for the development of cervical disease in these ethnic populations. The scant information collected so far for cervical cancer risks in New Mexico does not indicate unusual risk profiles for American Indian and Hispanic women with high rates of cervical disease. Comprehensive analytic studies focused on the high-risk minority women of this state are needed to provide information on the causes of cervical cancer in New Mexico.

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Articles

Acute Poisoning From γ-Hydroxybutyrate in California

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We report a series of 5 representative patients in California who experienced adverse reactions from the illicitly marketed substance γ-hydroxybutyrate (GHB). The drug is a putative neurotransmitter marketed as a growth hormone releaser for bodybuilders. The most commonly reported symptoms included abrupt drowsiness, dizziness, and a "high." Other effects were headache, nausea, vomiting, myoclonic jerking, and short-term coma. There have been no reported deaths. If product use is discontinued, full recovery with no long-term side effects is universal. No clear dose-response effect was observed; this may be attributable to differences in susceptibility, wide variations in doses taken by the same person, or the coingestion of other substances. Case interviews confirm that, despite being banned by the US Food and Drug Administration, GHB is still widely available in the underground drug market. Athletes and bodybuilders may take drugs for which there are claims of improved performance or body image. Physicians should be alert for signs of GHB poisoning in emergency department and clinic patients.

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On August 7, 1990, the San Francisco Regional Poison Control Center notified the US Food and Drug Administration (FDA) and the California Department of Health Services (DHS) of acute poisonings with gastrointestinal, respiratory, and central nervous system symptoms associated with the consumption of the illicitly marketed substance γ-hydroxybutyrate (GHB).[1] The drug is a putative neurotransmitter that was sold to bodybuilders as a "dramatic new growth hormone releaser." It was also marketed as a health aid to dieters and persons with insomnia. Three months later, on November 8, 1990, the FDA warned consumers to discontinue use of the illegally marketed substance. The state health departments of California and Florida issued similar warnings and banned the sale of GHB in their states. By November 30, 1990, there were 25 reported cases of acute poisoning related to GHB in California (17 from San Francisco); 15 cases in Georgia; 7 in Florida; 3 in South Carolina; 2 each in Arizona and Minnesota; and 1 each in Texas, Ohio, Virginia, and the District of Columbia.[1]

A paper summarizing the San Francisco cases has recently been published.[2] We describe in greater detail the histories of representative patients in whom adverse reactions were associated with the use of GHB. We compare the findings with information in the published literature and examine some of the issues implied by the case series. Table 1 summarizes some of the known product names and distributors of GHB.

Biochemistry and Metabolism

The natural metabolic role of GHB is not well understood, and the psychophysiologic effects are described in an extensive body of literature that is wide-ranging but inconclusive.

γ-Hydroxybutyrate (chemical formula $HOOC\text{-}CH_2\text{-}CH_2\text{-}CH_2OH$) is a four-carbon molecule that is found naturally in the central nervous system and, in higher concentrations, in peripheral tissues.[3] It has a structure much like γ-aminobutyric acid (GABA), which is better understood than GHB and acts as an inhibitory neurotransmitter in vivo. γ-Aminobutyric acid is catabolized by transamination to succinate semialdehyde, which is then oxidized to succinate[4] (Figure 1). Brain tissue is capable of reducing succinate semialdehyde to GHB. Concentrations of both GHB and GHB-oxidizing enzymes are 15 to 20 times higher in kidney, heart, skeletal muscle, and brown fat than in the central nervous system.[5] The significance of this finding is not known, however.

γ-Hydroxybutyrate exhibits the properties of a neurotransmitter in humans and has a wide range of purported pharmacologic effects.[6] Hippocampal receptors for GHB have been isolated; synaptic transmission and regulation have been demonstrated.[6] Nevertheless, some investigators think that GHB has not yet fulfilled all the criteria needed to be considered a bona fide neurotransmitter because its effects have not been associated with specific neuronal tracts. Research in this area continues.[6,7] γ-Hydroxybutyrate crosses the blood-brain barrier. Some studies have shown that it can double brain dopamine and dynorphin levels and that this pharmacologic effect can be blocked experimentally by naloxone, dextro-amphetamines, and caffeine.[8,9] Because it in-

TABLE 1.—*Products and Distributors of γ-Hydroxybutyrate*

Common Product Names	*Currently Known Distributors*
γ-Hydroxybutyric acid	Biosky
Sodium oxybate	Biotonic Formulary
Sodium oxybutyrate	Hi-Tech Bodybuilding
γ-Hydroxybutyrate sodium	
γ-OH	
4-Hydroxy butyrate	
γ-Hydrate	
Somatomax PM	

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ABBREVIATIONS USED IN TEXT

DHS = California Department of Health Services
FDA = US Food and Drug Administration
GABA = γ-aminobutyric acid
GHB = γ-hydroxybutyrate
REM = rapid-eye-movement

creases the level of dopamine in certain areas of the brain, GHB has been used experimentally to treat auxiliary symptoms of narcolepsy (such as myoclonus and cataplexy) associated with dopamine deficiency.

The role of GHB as an agent to increase muscle mass is ambiguous. Growth hormone release is known to be greater during slow-wave sleep, a pattern of sleep that is facilitated by GHB. This short-term effect (half-life approximately one to two hours) has been demonstrated by some investigators.[10] It is not clear what long-term effects this may have on actual muscle growth or mass.

The clinical effects of GHB are well documented—short-term amnesia and hypotonia with an oral dose of 10 mg per kg, and drowsiness and sleep with 20 to 30 mg per kg. γ-Hydroxybutyrate promotes rapid-eye-movement (REM) sleep in depressed and narcoleptic patients and induces non-REM sleep in normal persons.[11] Studies on the effects of anesthetic use in humans indicate that an intravenous dose of 50 to 70 mg per kg produces hypnosis but little analgesic effect.[12] The same dose may cause mild hypotonia, bradycardia, and bradypnea, as well as nausea, vomiting, and Cheyne-Stokes respiration. Typically, an intravenous dose of 65 mg per kg induces sleepiness within five minutes descending into a comatose state that lasts one to two hours or more, after which there is rapid awakening.[13] Higher doses may lead to severe cardiac and respiratory depression and other neurodepressive sequelae.[14,15] Studies in animals show that when plasma levels of GHB exceed 500 μg per ml, myoclonic seizures almost always result. (In humans, oral doses in mg per kg approximate plasma levels expressed in μg per ml.) No published trials have been carried out in humans at this dosage.

γ-Hydroxybutyrate may potentiate other endogenous opiates or exogenous narcotics, and it is potentiated by alcohol, benzodiazepines, and other neuroleptics.[15,16] While dextroamphetamine, naloxone, trimethadone, and valproate antagonize the electroencephalographic changes produced by GHB, no clinically effective GHB antagonists are consistently described in the published literature.

In light of these many important effects, it is important that physicians be familiar with the clinical picture that GHB poisoning presents.

Methods

As of November 28, 1990, 25 cases of GHB toxicity had been reported to poison control centers in California. Because of the nature of poison control center telephone consultations, information for retrospective follow-up is not always available. Follow-up information was obtained for only 14 of the 25 cases. In 10 of the 14 traceable cases, the patient or the physician was contacted successfully. All 10 contacts ultimately cooperated by either answering a telephone questionnaire or granting DHS access to the medical chart (Table 2). Five of these cases were previously summarized as index cases.[2*] This report gives more detailed information on five cases (two previously summarized and three new cases) that illustrate the spectrum of serious illness seen.

*Alfredo Quattrone, PhD, and Alan Slagle, PharmD, provided information on some of the index cases.

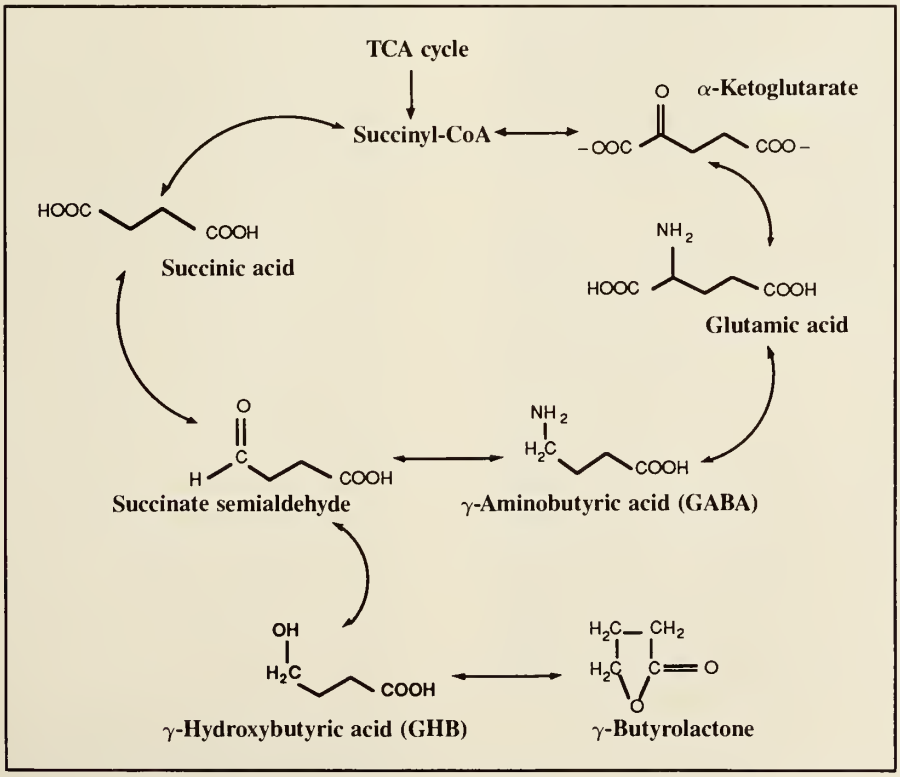

Figure 1.—The biochemical pathway of γ-hydroxybutyrate metabolism is shown. CoA = coenzyme A, TCA = tricarboxylic acid

TABLE 2.— *Summary of 10 Abstracted Cases Reported to California Poison Control Centers*

		Adverse Reaction															
Case	*Dose*	*Drowsiness*	*Dizziness*	*"High"*	*Headache*	*Confusion*	*Nausea*	*Vomiting*	*Diarrhea*	*Incontinence/ Urgency*	*Trouble Breathing*	*Uncontrollable Shaking*	*Temporary Amnesia*	*Seizure*	*Coma*	*Other**	*Other Substances Ingested*
1	Unknown	X	X	X	X	--	--	--	--	X	--	--	X	--	--	--	--
2	~2 tsp	X	X	X	--	X	--	--	--	--	X	X	--	--	--	X	Hydrocodone bitartrate and acetaminophen
3	Unknown	X	X	X	X	X	X	X	X	X	--	--	--	--	--	--	Alcohol
4	~1 tsp	X	--	X	X	--	X	--	--	--	X	X	--	--	--	--	--
5	Unknown	X	--	--	--	X	--	X	--	--	--	X	--	X	X	--	Alcohol
6	~1 tsp	X	--	X	--	--	--	--	--	--	--	--	X	X	--	--	--
7	4 tsp in 8 h	X	X	X	--	X	--	--	--	X	X	X	--	X	X	--	--
8	2 tsp	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--
9	1 tsp	X	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--
10	1.5 tsp	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	Diphenhydramine hydrochloride

*Hallucinations, moaning, or babbling.

Report of Cases

Case 1

A previously healthy 39-year-old woman bought GHB from a health food store and took a 1-teaspoon dose in September 1990. Within 10 minutes she experienced numbing of the legs, dizziness, and a tight chest. She was helped to bed and did not take GHB again for three weeks. Then she began taking a half-teaspoon of GHB granules in juice almost daily and did so for a month.

In one instance she took three or four doses during the course of a single day. The last dose, taken at bedtime, triggered the reported adverse response. She experienced a "high" (similar to the high she had experienced from past marijuana use), the "jabbers" (pressured speech and ebullience), intense drowsiness, confusion, difficulty breathing, and uncontrollable twitching in her arm. Her children reported that, when they found her, her eyes were rolled back, her body was tense, and she was hallucinating. Her medical chart indicates she was twitching for 45 minutes. She had no previous history of seizures.

She was seen in an emergency department and admitted to hospital overnight. Her pulse, blood pressure, and respirations were normal. A physical examination was unremarkable except for alternating wakeful and sleepy states with irregular leg twitches. Laboratory values included a leukocyte count of 10.8×10^9 per liter (10,800 per μl), hemoglobin 133 grams per liter (13.3 grams per dl), hematocrit 0.40 (40.3%), and thrombocyte count 258×10^9 per liter (258×10^3 per μl). Electrolyte levels were sodium 142, potassium 3.6, and chloride 104 mmol per liter. Bicarbonate, creatinine, and blood urea nitrogen levels were not noted in her chart, and no blood gas determinations were done. She was taking ibuprofen and a combination product containing hydrocodone bitartrate and acetaminophen (Vicodin) around the time she ingested GHB. Although she drinks alcoholic beverages and had previously used illicit drugs, she denied ingesting alcohol or using drugs when taking GHB. She experienced a full recovery with no lasting symptoms.

Case 2

The patient, a previously healthy 26-year-old woman who is a bodybuilder, acquired GHB from a friend at the gymnasium where she trained. On October 28, 1990, she took the dose recommended on the bottle (one scoop or about 1 teaspoon) and went to sleep; she was ill the next morning. Four days later, she attended a party and drank a glass of wine. Afterward, she took GHB again; she was ill that night and for the next two days. She experienced vomiting, drowsiness, headache, nausea, diarrhea, confusion, dizziness, a "high" ("felt like Quaaludes or Valium"), and intermittent lack of bladder control. She did not go to a hospital and was not seen by a physician. She had no history of medical problems. At the time she took GHB, she was taking birth control pills and was otherwise "totally drug free." Since discontinuing GHB, she has been asymptomatic.

Case 3

The patient, a 28-year-old woman, was at a nightclub when she ingested GHB with some mixed drinks. She experienced confusion and uncontrollable shaking, followed by a seizure and then coma. A witness stated that she was banging her head on a wall before becoming unconscious. The patient vomited and was suctioned before being transported to hospital. Paramedics reported that she alternated between combativeness and unresponsiveness during transport.

She arrived in the emergency department with good respiratory effort but long apneic periods. On admission, she was restrained, intubated, ventilated, lavaged, and given activated charcoal. Laboratory values included a leukocyte count of 10.9×10^9 per liter (10,900 per μl), hemoglobin 119 grams per liter (11.9 grams per dl), hematocrit 0.37 (36.9%), and thrombocyte count 306×10^9 per liter (306×10^3 per μl). Blood chemistry values included sodium 143, potassium 3.9, bicarbonate 30, and chloride 110 mmol per liter; creatinine 88.4 μmol per liter (1.0 mg per dl); and blood urea nitrogen 3.57 mmol per liter (10 mg per dl). Initial arterial blood gas determinations with 95.5% oxygen saturation were pH 7.56, HCO_3 19.8 mmol per liter, P_{CO_2} 21.9 mm of mercury, and P_{O_2} 292.8 mm of mercury. Radiographic, electroencephalographic, computed tomographic, and magnetic resonance imaging scans were unremarkable. Past medical problems included anemia, asthma, and migraine headaches. The patient's toxicologic screen was negative, but her blood alcohol level was 80 mg per dl. No

adverse effects have been observed since she stopped taking GHB.

Case 4

A 47-year-old man bought GHB at a health food store after receiving a mailer advertising its effectiveness as a soporific. He said he took 1 teaspoon with a potassium supplement and water "every once in a while" for approximately two months. One day he took 1 teaspoon every two hours for a total dose of 4 teaspoons. Approximately a half hour after his last dose, his wife found him immobile and having difficulty breathing. Other symptoms included heavy drowsiness, confusion, a "high," urinary urgency, uncontrollable shaking (paramedics noted seizure), dizziness, and coma. The patient noted that on other occasions GHB had made him more talkative. In the emergency department he was initially lethargic but later became awake and alert. His physical examination, laboratory work, electrocardiogram, and contrast computed tomographic scan were normal, and he was released three hours later. A follow-up neurologic examination two weeks later was normal, with no focal findings and a normal electroencephalogram. The patient has had no symptoms since discontinuing GHB use.

This patient may have had a seizure 20 years ago after drinking excessively and taking a "few pills." He was seen by a physician at that time and had a normal electroencephalogram. He took no medications, is not aware of any other seizures in his life, and has no family history of seizures. His neurologist noted that his general health has been excellent and he has had no significant head injuries or fainting spells.

Case 5

The patient, a 23-year-old man, took 1 teaspoon of GHB as a growth hormone releaser. Four hours later, he was brought into the emergency department vomiting and unresponsive except to pain. His pupils were small and sluggish. On admission his blood pressure was 150/90 mm of mercury, pulse 60 beats per minute, and respirations 16 per minute. The physical examination was unremarkable and the laboratory findings undiagnostic. At this time a complete blood count revealed a leukocyte count of 12.3×10^9 per liter (12,300 per μl), hemoglobin 148 grams per liter (14.8 grams per dl), hematocrit 0.425 (42.5%), and thrombocyte count 196×10^9 per liter (196×10^3 per μl). Electrolyte levels were sodium 145, potassium 4.0, bicarbonate 5, and chloride 108 mmol per liter; creatinine 88.4 μmol per liter (1.0 mg per dl); blood urea nitrogen 5.35 mmol per liter (15 mg per dl); and glucose 11.4 mmol per liter (206 mg per dl). Arterial blood gas determinations with 97% oxygen saturation were pH 7.44, P_{CO_2} 43 mm of mercury, P_{O_2} 83 mm of mercury, and HCO_3 29 mmol per liter. Repeat electrolyte measurements four hours later indicated no significant changes except for an elevated bicarbonate of 32 mmol per liter. There was no evidence of alcohol or drugs in his blood or urine. The patient was discharged asymptomatic six hours after admission.

Case 6

In addition to the cases reported to the California poison control centers, DHS reports the case of a 77-year-old man who died in October 1990 of massive gastrointestinal hemorrhage caused by esophageal varices and marked fatty metamorphosis of the liver. In addition to various other over-the-counter medications (tryptophan, Prostex, Motion Mate, and Nutrasleep), he was also taking GHB. He was advised to do so by a health food store clerk who suggested it would restore the muscle tone that the patient perceived he was losing. It is unclear whether the GHB played a role in his death.

Discussion

These cases illustrate the adverse reactions associated with the uncontrolled, self-directed use of GHB in varying doses. Table 2 summarizes the symptoms recorded in 10 abstracted cases reported to California poison control centers.

No reliable estimate of GHB consumption in the general population is available. The number of cases with adverse reactions reported is likely to be only a fraction of the actual number of such cases and even a smaller fraction of all users. Indeed, some patients who were contacted indicated that they had experienced unreported adverse reactions before the incident that precipitated the case report.

There appears to be a tremendous potential for abuse of GHB as an illicit drug. All interviewed patients reported a pleasurable sensation or "high." Several explicitly noted that one reason they continued taking the drug was because it made them "feel good." At least one said that, as of December 1990, some of her friends could still obtain GHB "underground" (prices range from $50 to more than $80 for a 100-gram bottle). In the eastern United States, GHB is already gaining popularity as an illicit street drug. In addition, GHB has been marketed for young people and athletes. The abuse of steroids among persons seeking improved body image or athletic performance is well documented[17,18] and has created a lucrative and growing market for these substances. Finally, the case of the 77-year-old man who was taking GHB to improve a body ravaged by age and disease illustrates that the vulnerable population may not be restricted to the young.

Researchers working with narcoleptic patients consider GHB a relatively harmless and effective drug. Several points, however, must be kept in mind. First, and perhaps most important, the therapeutic effects of GHB for a person with narcolepsy—the induction of major symptoms of narcolepsy at night, when they can be better controlled—are considered adverse effects in a normal person. Second, the side effects, termed "mild" by researchers comparing them to the extreme debilitation caused by narcolepsy, would be considered unacceptable in a normal person. Third, differences between normal and narcoleptic persons also may account for the different reactions to equivalent doses, although responses to equivalent doses vary considerably even for the same person. Fourth, the quality (reagent vs pharmaceutical grade) and quantity of GHB ingested is rigorously controlled and monitored in clinical trials. For casual users, however, there is no accurate method of assessing the amount or quality of GHB consumed. No doubt the actual size of a reported "1-teaspoon" dose varied widely.

Early suspicions that the adverse reactions were caused by contamination of retail lots seem unfounded. The symptoms experienced are compatible with documented physiologic effects of GHB. Toxicologic screens and the clinical course of the patients admitted to hospital seem to rule out the diagnosis of exposure to other known drugs. One lot of GHB recovered by the FDA was analyzed using capillary and

column gas chromatography. The results indicated that GHB was present as a sodium salt at 97% to 98% purity.

Conclusions

The drug GHB is a substance with documented clinical actions consistent with severe neurotoxicity. In many cases, intensive medical care has been required to counteract adverse reactions. Health professionals must understand that, despite FDA interdiction, this substance is still available to, marketed for, and used by bodybuilders, dieters, and persons suffering from insomnia. Patients should be told that compounds bought in health food or natural food stores may be drugs that can substantially alter body functions and adversely affect health. There are now over 40 reported cases of GHB poisoning in California (and additional cases in other states), and several of the persons involved in these cases procured the substance since it was banned on November 8, 1990.

The prognosis for those who experience GHB poisoning is quite good. There are no documented or anecdotal reports of long-term adverse effects or fatalities, nor any evidence for physiologic addiction. Current investigative efforts are directed toward interdiction, continued case surveillance with clinical description, additional study to understand how widespread GHB use may be, and efforts to disseminate accurate information regarding the adverse health effects of illicit GHB use.

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Articles

Clinic-Based Primary Care of Frail Older Patients in California

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We surveyed medical directors of primary care clinics in California to learn how those clinics cared for their frail older patients. Of 143 questionnaires sent, 127 (89%) were returned. A median of 30% of all patient encounters were with persons aged 65 or older, and a median of 20% of older patients were considered frail. A total of 20% of the clinics routinely provided house calls to homebound elderly patients. Of clinics involved in training medical students or physicians (teaching clinics), 70% had at least one physician with an interest in geriatrics, compared with 42% of nonteaching clinics ($P < .005$). For frail patients, 40% of the clinics routinely performed functional assessment, while 20% routinely did an interdisciplinary evaluation. Continuing education in geriatrics emerged as a significant independent correlate of both functional assessment and interdisciplinary evaluation. Among the 94 clinics with a standard appointment length for the history and physical examination, only 11 (12%) allotted more than 60 minutes for frail patients. The data suggest that certain geriatric approaches are being incorporated into clinic-based primary care in California but do not provide insight into their content or clinical effects.

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Older Americans who receive health care as outpatients tend to be burdened with multiple chronic illnesses. Those aged 70 years and older carry a mean of 5.6 diagnoses, compared with 3.6 for patients younger than 70.[1] Many are functionally impaired. At least 10% of persons aged 65 and older require assistance with personal care activities such as bathing, dressing, and walking.[2] Of those older than 74, 15% are homebound. Older patients also visit their physicians more often.[3,4] In 1981 persons aged 75 years and older comprised 13% of outpatient visits to internists' offices.[5] As their number is predicted to nearly double by the year 2000,[6] their contribution to outpatient visits can be expected to rise substantially.

Experts in geriatric medicine advocate that good health care of older adults requires that physicians have specific medical knowledge of the aging process and adopt a clinical approach that takes into account the greater prevalence of chronic disease, functional impairment, and the need for social supports among this population. Fundamental tenets of geriatric clinical practice include comprehensive functional assessment, interdisciplinary evaluation, and the need for longer appointments with older patients.[7-10]

The systematic assessment of patient functioning among targeted older patients in certain clinical settings has been shown to enhance diagnostic accuracy, prolong survival, reduce the use of acute-care hospitals and nursing homes, and reduce annual medical care costs.[11-13] In 1988 the American College of Physicians formally adopted the position that comprehensive functional assessment should be an integral part of internists' armamentarium in the management of older patients.[14] A second tenet of geriatric practice holds that successful health care of frail older adults requires the close collaboration of physicians and allied health professionals.[9,10,15] In addition, relatively more time is required to evaluate frail older patients.[8] The rationale for longer appointments is both medical and logistic. Frail patients tend to have multiple medical, functional, and psychosocial problems that require careful history taking. This may necessitate additional questioning of a family member or care giver. These patients may also have sensory impairments that slow communication, physical impairments that hinder the performance of the physical examination, or both.

Little is known about the quality of health care for the elderly or the extent to which the knowledge and principles of geriatric medicine have become incorporated into clinical practice. Using data from the 1971-1975 Health and Nutrition Examination Survey, Heller and colleagues retrospectively evaluated the quality of care for patients aged 65 to 74 years for five target conditions.[16] Although they identified low income as a significant correlate of deficient care, they were unable to shed light on the processes contributing to good or bad health care. In assessing the management of older patients in 15 university-based internal medicine practices, Siu and associates[17] found that the common geriatric diagnoses of dementia, osteoporosis, and incontinence were mentioned far less frequently than would have been expected from the prevalence of these conditions in the older population, suggesting that house officers and their preceptors failed to recognize the presence of these conditions. An analysis of test-ordering behavior among primary care physicians, based on survey data from 1976 through 1978, also suggests a prevailing lack of knowledge of geriatric medicine.[18] Finally, physicians, including those in primary care, have tended to spend less time with their older patients,[19-21]

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ABBREVIATIONS USED IN TEXT

CME = continuing medical education
HMO = health maintenance organization
VA = Department of Veterans Affairs

although the mean duration of visits may increase for very old patients.[22]

Since 1981, the number of fellowship-trained geriatricians, whose presence should help disseminate geriatric knowledge, has increased.[23] We describe the extent to which primary care clinics in California by mid-1987 had incorporated geriatric approaches such as functional assessment, interdisciplinary evaluation, and longer appointments for the frail elderly. We also describe the prevalence of special services such as house calls and case management. Finally, the distinguishing characteristics of those clinics that incorporated these services and geriatric principles are examined.

Methods

We conducted a mail survey of primary care clinics in California that inquired about the process of care for their frail elderly patients. We chose California as the site for our survey because it has the largest elderly population in the nation[24] and has been a leader in providing services for the elderly at the state level. According to the 1980 US Census, California had 2.4 million adults aged 65 years and older, of whom 39% were older than 74.[25] We selected outpatient clinics and excluded physicians operating from private offices, under the rationale that clinics tend to be larger organizations than private offices and therefore are more likely to offer special services such as case management.

Identification of Adult Primary Care Clinics

We subdivided outpatient clinics into five mutually exclusive types: private hospital outpatient departments, county-run (public) hospital outpatient departments and clinics, private community clinics, multispecialty group practices, and Department of Veterans Affairs (VA) clinics. Possible survey sites were identified using the American Hospital Association's *Guide to the Health Care Field,*[26] the *American Group Practice Association Directory,*[27] and a listing of all licensed health facilities in California.[28] Staff-model health maintenance organizations (HMOs) with a Medicare contract were identified separately from a list provided by the Region IX office of the Health Care Financing Administration. All potential sites were entered into a data base and cross-checked by site name, address, and medical director to eliminate redundancy. From these sources we identified 467 separate, licensed outpatient facilities. These facilities were screened according to the following eligibility criteria:

- The clinic had to be located in a county with at least 5,000 persons aged 75 years and older according to the 1980 US Census.[25] This exclusion was based on the assumption that individual clinics in rural counties would see relatively few frail, older patients (defined as persons aged 75 years or older who have multiple chronic diseases or need assistance with personal care or both). To corroborate this assumption, we contacted ten randomly selected rural clinics that met the remaining selection criteria. Each estimated that 5% or fewer of their elderly patients met the definition of "frail." We exempted county-run outpatient clinics, academic medical centers, and VA ambulatory care centers from meeting this criterion because these facilities often act as regional health centers, attracting patients from a wide geographic area.
- The clinic had to provide primary medical care to adults in one of the primary care specialties of family practice, general practice, geriatrics, or internal medicine.
- The clinic had to have a medical director and at least one other full-time-equivalent primary care physician.
- The medical director or a designee had to profess knowledge of the clinic's patient population and practice patterns.

Of the 231 hospitals initially identified as having outpatient departments, 164 were excluded because those departments were ambulatory surgical centers, emergency departments, dental clinics, counseling centers, or obstetric clinics; were not regularly staffed by physicians; or were no longer in operation. Of the 236 nonhospital clinics, 71 were in counties with fewer than 5,000 persons older than 74. In the 1980 census, these excluded counties included 6% of Californians aged 75 years and older. An additional 37 clinics offered specialty services rather than primary medical care (dentistry, psychiatry, social services, or family planning). Six were staffed by one or no physician, 43 had no medical director, and 3 had medical directors unfamiliar with the practices of the other providers. The medical directors or designees of the remaining 143 outpatient clinics were sent questionnaires.

Survey Instrument

We developed a 76-item questionnaire regarding clinic and patient characteristics and the providers, services, and process of care for the clinic's frail elderly patients. The medical director of each eligible site was contacted by telephone to solicit participation in the survey. The medical director, or a designee identified at the time of telephone contact, was then mailed a copy of the questionnaire. Because we collected data based on report rather than on direct observation of practice, we took several measures to improve the accuracy of information. First, the questionnaire was sent to the person identified as being most knowledgeable about the clinic's patient population and practice patterns. Second, definitions were furnished for terms that could have been ambiguous for some respondents (Figure 1). Third, most questions included the response option of "uncertain" to eliminate guessing. Fourth, questionnaires were anonymous to encourage candid responses.

To assess test-retest reliability of the questionnaire, we sent duplicate surveys to 20 respondents who agreed to complete a second questionnaire; 18 were returned. We sent the second questionnaire three weeks after receiving the original to minimize any carry-over effect.[29] We defined test-retest reliability as identical answers in at least 85% of the pairs for categoric and ordinal-scale questions, and within 10% in at least 85% of the pairs for numeric estimates. Only the data for those questions that met the above criteria were included in the analysis.

Statistical Analysis

The data were analyzed using conventional descriptive statistical methods. For continuous and interval data, parametric statistics were used. Nonparametric statistics were employed for data based on ordinal scales or when normal

distribution of the sample was not approximated. For correlations, the Pearson product-moment was used for continuous or interval data that approximated a normal distribution, and the Spearman rank correlation coefficient was used for skewed continuous or interval data. We employed the Kendall's τ correlation coefficient if one or both of the variables were ordinal. Stepwise multiple regression was used to examine the relative effect of variables on selected geriatric practices, such as functional assessment, and to determine the amount of variance in these practices explained by the variables. For the regression models, we set $P = .05$ as the significance to enter. Because of the number of statistical tests done, we established statistical significance for all other analyses at $P < .01$. Data were analyzed on a personal computer using the statistical software package SPSS-PC+ (SPSS, Inc, Chicago, Ill).

Definitions Provided in the Questionnaire

Case Management The process of assessing needs, identifying resources, and coordinating and monitoring the delivery of services for frail older persons by a health professional.* Case management includes, but is not limited to, health care.

Fee-for-Service Clinic A clinic that bills the patient or a third-party insurer for services rendered and has fewer than 50% of its patients enrolled in a prepaid health plan.

Frail Elderly Persons aged 75 years and older who have multiple chronic diseases and/or need assistance in personal care.

Functional Assessment The systematic assessment of activities of daily living, instrumental activities of daily living, and mental status.

Health Maintenance Organization A clinic in which more than 50% of its patients belong to a prepaid health plan.

Interdisciplinary Evaluation The use of the independent findings of 2 or more health disciplines (such as medicine and nursing) in the formulation of the plan for patients' diagnosis and treatment.

Medicare Assignment A contract between physicians and the Health Care Financing Administration (HCFA), in which the "allowed" charge (as determined by HCFA for a Medicare visit under Part B) is accepted as payment in full. A physician signing such a contract is said to be "participating."† (For this study, a nonparticipating physician also is considered to accept assignment, provided the "allowed" charge is accepted as payment in full for at least 80% of Medicare visits.)

Medicare-Contract Health Maintenance Organization (HMO) An HMO that has established a risk-based contract with HCFA for capitated health care of Medicare patients, as provided by the Tax Equity and Fiscal Responsibility Act of 1982.‡

Definitions of Variables

Geriatrics Consultation An ordinal "dummy" variable for the amount of activity the clinic devotes to geriatric consultations.

Primary Care An ordinal "dummy" variable for the amount of activity the clinic devotes to ongoing (long-term) primary care, as opposed to a single or limited contact with a patient for the purpose of consultation or the management of an acute illness.

Teaching Clinic A clinic involved in graduate and/or postgraduate medical education. This categoric "dummy" variable encompasses the responses to two separate questions in the survey. A clinic is considered to be involved in the clinical education of physician trainees if it devotes a moderate to large amount of its activity to teaching clinical geriatrics to fellows, residents, or medical students, or has at least 2 full-time-equivalent fellows or residents staffing the clinic whenever it was open, or both.

*R. W. Besdine, "Approach to the patient," *In* J. C. Beck (Ed): *Geriatrics Review Syllabus: A Core Curriculum in Geriatric Medicine*, Book 1. New York, NY, American Geriatrics Society, 1989, pp 20-29.

†*1986 Medicare Explained.* Chicago, Ill, Commerce Clearing House, Inc, 1986.

‡*American Group Practice Association Directory.* Alexandria, Va, American Group Practice Association, 1984.

Figure 1.—Definitions of terminology used in the study.

Results

Response Rate and Handling of Nonresponses

Of the 143 questionnaires sent, 127 were returned, for a response rate of 89%. Of the 16 nonrespondents, 2 were from hospital outpatient departments and 12 were from multispecialty group practices, 5 of which were affiliated with Medicare-contract HMOs. Individual item nonresponses occurred in as many as 16% of returned questionnaires. Because of the high overall return rate, we chose not to impute missing data. When there is a high overall response rate, such a procedure does not produce a substantial gain in accuracy and may increase the variance of the means that are computed using imputed values.[30] When an item nonresponse occurred in ten or more questionnaires, we screened for bias by comparing respondents and nonrespondents based on clinic type, funding source, and teaching status. There was no significant difference between respondents and nonrespondents in any of these cases. Because of item nonresponses, the denominators for some of the statistical analyses reported below are less than the total number of questionnaires returned.

Patient and Clinic Characteristics

A median of 30% of all clinic visits were from patients aged 65 and older. Of these patients, a median of 20% were considered frail, a median of 10% were homebound, a median of 5% resided in a skilled nursing facility, and a median of 60% were considered poor. Table 1 shows the distribution of respondents by clinic type and special characteristics or services. Of the clinics, 61 (48%) had at least a part-time social worker on the premises. Of the 93 respondents in fee-for-service clinics, 4 were "uncertain" whether their clinic physicians accepted Medicare assignment. Of the remaining 89, 69 (78%) indicated that all of their physicians accepted Medicare assignment. Not surprisingly, clinics with physicians interested in geriatrics had a larger mean percentage of patients older than 64 ($P < .01$). Of the 67 clinics involved in graduate and postgraduate medical education (teaching clinics), 47 (70%) had at least one physician interested in geriatrics, compared with 25 (42%) of the 60 nonteaching clinics ($P < .005$). Because of the survey design, interest in geriatrics by primary care specialty could not be broken down. All but 2 of the 29 clinics with one or more fellowship-trained geriatricians were teaching clinics.

Of the 127 respondents, 28 were uncertain about whether physicians at their institutions had received continuing medical education (CME) in geriatrics within the previous two years. For the remaining 99, 51 (52%) indicated that most or all of their physicians had had CME in geriatrics, while 48 (48%) indicated that none or a few had. Recent CME in geriatrics was not more prevalent either in clinics with physicians interested in geriatrics or in teaching clinics. The prevalence of CME correlated slightly with the percentage of older patients considered frail (Kendall's $\tau = .24$, $P = .003$). Among the 22 clinics with more than 45% of older patients meeting the criteria for frailty, 6 (27%) had no physicians

TABLE 1.—*Characteristics of the Responding Clinics*

Clinic Type	N	Clinic Characteristics: Teaching*	Nonteaching	> 50% of Patients > 64 yr No. (%)	Has Trained Geriatrician No. (%)	Physicians Interested in Geriatrics No. (%)	Routine House Calls* No. (%)	Case Management† No. (%)
Private hospital outpatient department	53	31	22	14 (26)	10 (19)	27 (51)	10 (19)	17 (32)
County-run clinic	15	11	4	4 (27)	4 (27)	9 (60)	4 (27)	5 (33)
Private community clinic	18	4	14	5 (28)	1 (6)	9 (50)	4 (22)	4 (22)
Multispecialty group practice	28	11	17	8 (29)	6 (21)	17 (61)	6 (21)	4 (14)
Veterans Affairs clinic	13	10	3	11 (85)	8 (62)	10 (77)	2 (15)	8 (62)
TOTALS	127	67	60	42 (33)	29 (23)	72 (57)	26 (20)	38 (30)

*At least 50% of the time, homebound patients are seen at home by clinic physicians or physician extenders, rather than having the patient brought to the clinic.
†Case management is defined in Figure 1.

with recent CME in geriatrics, compared with 41 of 77 clinics (53%) with less than 45% frail patients ($P = .003$). Continuing medical education in geriatrics also correlated significantly with the performance of functional assessment (Kendall's $\tau = .35$, $P = .0001$) and interdisciplinary evaluation (Kendall's $\tau = .48$, $P < .0001$).

Special Services for the Frail Elderly

Of the respondents, 26 (20%) reported that their clinics routinely (more than 50% of the time) furnished medical care to their homebound older patients through house calls by clinic physicians or physician extenders, rather than requiring homebound patients to be brought to the clinic. The frequency of house calls correlated to some extent with the percentage of clinic patients who were homebound but did not reach our cut-off statistical significance (Kendall's $\tau = .25$, $P = .03$). The frequency of house calls was similar in teaching and nonteaching clinics. House calls also occurred with equal frequency in clinics with and without physicians trained or interested in geriatrics.

A total of 41 (33%) of the respondents indicated that their clinics provided case management by a nonphysician (Figure 1). Case management was used in 43% of teaching clinics compared with 22% of nonteaching clinics, but this difference exceeded our cutoff for statistical significance ($P = .022$). While case management was reported more frequently in those clinics having at least a part-time social worker ($P < .01$), its use was unrelated to the percentage of elderly patients considered frail.

The frequencies of case management and house calls were similar in clinics with different funding sources (fee for service, capitation, or federal government) and in different types of clinics (community hospital outpatient department, county clinic, private community clinic, multispecialty group practice, or VA).

Geriatric Approaches to the Frail Elderly

We looked at the frequencies of functional assessment and interdisciplinary evaluation and at which variables independently correlated with their application. For functional assessment, 14 respondents selected "uncertain," leaving a valid denominator of 113. Of these, 20 (18%) indicated that functional assessment was never done, 38 (34%) indicated that it was "sometimes" done, and 45 (40%) indicated that their clinics almost always did a functional assessment when evaluating frail older patients. In all, 119 medical directors were able to estimate the frequency of interdisciplinary evaluation. Of those, 59 (50%) indicated that none of their physicians used this approach, 36 (30%) indicated that some of their physicians used it, and 24 (20%) indicated that all of their physicians followed an interdisciplinary approach.

Using stepwise multiple regression, we developed models to explain the variance in the use of functional and interdisciplinary assessment in our sample of clinics (Table 2). Variables were chosen that had significant univariate correlation with either functional assessment or interdisciplinary evaluation or that might influence their use. The variables entered into the regression models are listed and defined in Table 3. The variables "CME in geriatrics" and "interest in geriatrics" emerged as the significant indepen-

TABLE 2.—*Results of Stepwise Multiple Regression of Selected Variables* Against Geriatric Approaches to the Frail Elderly*

Geriatric Approach	Variance Independent Correlates	P	Explained, %
Functional assessment	CME in geriatrics	<.0001	30
	Interest in geriatrics	<.01	7
Interdisciplinary evaluation, model 1†	Geriatric consultation	=.001	25
	Length of history and physical examination	<.01	8
	CME in geriatrics	<.01	6
Interdisciplinary evaluation, model 2†	Percentage of older patients considered frail	<.001	17
	CME in geriatrics	<.05	7
	Teaching	<.05	3
Longer history and physical examination	Percentage of older patients considered frail	<.05	20
	Primary care	<.001	6
	Percentage of visits from patients ≥ 65 yrs	<.01	6

CME = continuing medical education

*See Table 3 for list of variables and their definitions.
†See text for details.

TABLE 3.—*Variables Entered Into Regression Models*

Variable	*Definition*
Capitation	Categoric variable (0,1) for clinics with income based principally on capitation*
CME in Geriatrics	Continuing medical education in geriatrics within previous two years
Federal government	Categoric variable (0,1) for clinics with income based on funds provided by the Veterans Affairs
Fee for service	Categoric variable (0,1) for clinics with income based principally on fee for service*
Geriatric consultation	Ordinal variable for amount of activity clinic devotes to geriatric consultations*
Interest in geriatrics	Expressed interest or advanced training in geriatric medicine by 1 or more clinic physicians
Length of history and physical examination	Standard scheduled length of history and physical examination†
Percentage of older patients considered frail	Percentage of patients older than 64 considered frail*
Percentage of visits from patients ≥ 65 yr	Percentage of all patient encounters made up by persons aged 65 and older
Primary care	Ordinal variable for amount of activity clinic devotes to ongoing primary care*
Teaching	Categoric variable (0,1) for clinics involved in graduate and postgraduate medical education*

*Terms used are defined in Figure 1.
†See text for further explanation.

dent correlates of functional assessment. We developed two models to explain performance of an interdisciplinary evaluation (Table 2). The first includes all clinics and explains 39% of the variance. The triad of comprehensive geriatric assessment, longer appointments, and interdisciplinary evaluation is expected in a geriatric assessment clinic, however, causing us to be concerned that the inclusion of geriatric clinics might have biased this regression model. To adjust for this influence, we developed a second model that excluded the 21 clinics in which at least 80% of patient visits were from persons aged 65 and older. The revised model retains the variable "CME in geriatrics" but explains only 27% of the variance.

The distributions for the preset length of a history and physical examination and a return appointment are shown in Table 4. One of 8 Medicare HMOs, 3 of 18 regular HMOs,

TABLE 4.—*Standard Scheduled Appointment Lengths for Frail Older Patients*

Type of Appointment	*Length, min*	*Patients No.*	*(%)*
History and physical examination, $n=94$*	≤30	34	(36)
	31-60	49	(52)
	61-90	7	(7)
	>90	4	(4)
Return appointment, $n=87$†	≤15	27	(31)
	16-20	30	(34)
	21-30	25	(29)
	>30	5	(6)

*The individual physician was allowed to set length of history and physical examination by 33 (26%) of the clinics.
†The individual physician was allowed to set length of return appointment by 40 (31%) of the clinics.

and 29 of the 101 fee-for-service or VA clinics indicated that the individual practitioners set their own appointment lengths for the history and physical examination. In addition, 40 (31%) of the respondents indicated that individual practitioners determined the duration of the return appointment. Because of the survey design, the average time these physicians spent on history taking and physical examinations for their frail patients could not be determined.

The preset length of the history and physical examination did not differ significantly by type of clinic but did differ significantly among clinics with different funding sources (fee for service, capitation, or VA; Kruskal-Wallis analysis of variance, [ANOVA] $P < .01$). Of the HMOs, 5 (23%) had appointment lengths greater than 45 minutes, compared with 31 (44%) of the fee-for-service and VA clinics ($P < .01$). Overall, the duration of a history and physical examination correlated significantly with the percentage of older patients considered frail (Spearman rank correlation coefficient = .44, $P < .0001$). This correlation persisted after adjusting for funding source. There was a trend toward longer appointments in teaching clinics ($P = .02$). Among the 11 clinics allotting more than 60 minutes for a history and physical examination, 5 were hospital outpatient departments, 2 were VA clinics, and 4 were community clinics, of which one was a Medicare-contract HMO.

We sought to explain the variance in the duration of a history and physical examination using stepwise multiple regression. Three independent correlates emerged: "percentage of older patients considered frail," "primary care," and "percentage of visits from patients ≥ age 65" (Table 2). Of note is that "primary care" (amount of activity devoted to long-term primary care) correlated *inversely* with appointment length. For the return appointment, there was a trend toward longer standard lengths in teaching clinics ($P = .03$) but no significant correlation with either the percentage of encounters with patients aged 65 and older or the percentage of patients aged 65 and older who were frail.

Discussion

The findings of this survey reflect reported approaches to the care of older patients by licensed primary care facilities in California in 1987. The data provide insight into the process of care for frail older patients in the clinic setting, which constitutes an important segment of the primary care delivery system. Because of the relatively small number within each clinic category, however, we caution against generalizing about the different types of clinic. The overall findings may not pertain to clinic trends in other states, where different health care environments prevail.

Our survey found that a median of 30% of all patient encounters were with persons aged 65 years and older. This percentage is consistent with other studies of outpatient primary care of the elderly.[4,5,17] The percentage of clinic patients older than 64 living in nursing homes (median 5%, mean 7%) is similar to the percentage of persons older than 64 who reside in nursing homes nationwide (5%).[31] The high median percentage of older patients considered poor (60%) contrasts sharply with the nationwide statistic of 12.6% of persons older than 64 who lived below the poverty line in 1985.[24] Our finding, however, is consistent with previous observations that patients attending clinics—especially hos-

pital outpatient departments—tend to have a lower socioeconomic status than those attending private offices.[32]

In California, the percentage of participating physicians for Medicare assignment has been increasing annually, rising from 31% in 1984 to 48.5% in 1988 (A. Blake, Chief of External Affairs, Health Care Financing Administration—Region IX Office, oral communication, Nov 1989). By comparison, 78% of the fee-for-service clinics sampled in our survey accepted assignment in 1987. Part of the difference may be due to our liberal definition of assignment: Nonparticipating physicians who accepted Medicare's allowed charge for at least 80% of Medicare visits were considered to accept assignment. Nevertheless, the findings do suggest that per-visit, out-of-pocket expenses for outpatient physician services may be less, on average, in medical clinics than in private offices. The medical clinic, therefore, may be an attractive alternative for Medicare recipients unable to afford charges above the 20% Medicare co-payment. Further research is needed to confirm this interpretation.

Overall, only 20% of the clinics surveyed routinely provided house calls to homebound older patients. Providing house calls was not influenced by either teaching status or the presence of physicians with interest or training in geriatrics. This low figure raises concern about whether homebound clinic patients receive adequate health care. Up to 40% of those older than 85 years are rendered homebound by impaired mobility,[3] and this age group is the most rapidly growing segment of the US population[6,33]; thus, the number of frail, homebound patients needing primary health care can be expected to increase well into the next century.

Case management may be especially useful for frail older patients because of their relatively high dependency and the corresponding need for multiple services. A case manager, working with other health professionals, identifies the need for services, coordinates the delivery of services, and monitors the patients' care.[34] Although de facto case management is often carried out by primary care physicians, it is time-consuming and not in the traditional purview of medicine. The presence of a nonphysician case manager reflects the importance of this activity in the care of frail patients, as well as the willingness of physicians to delegate this responsibility to others. Not surprisingly, the occurrence of case management was related to the presence of a social worker in the clinic. For frail elderly persons, the availability of a social worker may be an important advantage of attending a clinic rather than a private office. Although physicians operating from private offices can refer a patient to a home health agency for social work assessment, Medicare will reimburse the home health agency for these social services only as part of a limited evaluation visit or while the patient is receiving skilled nursing or restorative therapy from the agency.[35]

The frequencies of the use of functional assessment and interdisciplinary evaluation were unexpectedly high. Although misinterpretation of the questions or a desire to impress the surveyors (whose cover letter was on university stationery) could have influenced these results, the definitions provided in the questionnaire were straightforward and all questions used in the data analysis met reliability criteria. If accurate, these observations support the hypothesis that geriatric approaches to clinical care are diffusing beyond academic medical centers into everyday clinical practice. Our data, however, do not provide information about the content of the functional and interdisciplinary assessments, how they influenced clinical decision making, or whether their use affected patient outcomes.

After adjusting for the interaction of other variables, only CME in geriatrics and an interest in geriatric medicine remained significant correlates of the application of functional assessment. Only 9% of the clinics that had "few" physicians with CME in geriatrics routinely did functional assessments. In contrast, 56% of the clinics in which "most" physicians had had CME performed functional assessments on a routine basis ($P < .0001$). Continuing medical education in geriatrics also stood out as the only explanatory variable common to the two regression models for interdisciplinary evaluation. These associations held despite the fact that only the presence or absence of geriatric CME, rather than the total number of hours, was asked. Because most continuing education classes in geriatrics do not explicitly teach functional or interdisciplinary assessment, it is unclear how CME promoted these clinical approaches. Possibly CME served as a marker for another explanation—for example, that persons who attend postgraduate education in geriatrics also read the geriatric medical literature. Nevertheless, the association of CME in geriatrics with geriatric approaches to clinical care underscores a need for medical societies and schools to increase the number of CME courses devoted to geriatrics. In recent years, these have made up only about 1% of all CME courses.[15]

Clinics devoted to following a patient over the long term—as opposed to limited encounters for the management of an acute illness or consultation on a referral—reported relatively shorter appointments for the history and physical examination. This somewhat paradoxical finding corroborates previous research suggesting that the duration of medical encounters with physicians decreases slightly as patients get older.[19-21] On average, older patients make more visits to physicians than younger patients.[4,6] A possible explanation for the negative correlation is that these primary care clinics divide the history and physical examination into several visits rather than completing it in one long session.

Because of the small number of staff-model HMOs identified in the survey, broad generalizations about their care of the frail elderly cannot be made. Payment source—capitation, fee for service, or federal government—did not influence the use of functional or interdisciplinary assessment, case management, or house calls. The HMOs had statistically shorter appointments than the fee-for-service or VA clinics, however, and only 15% of HMOs allowed their physicians to set their own appointment lengths. Although longer appointments constitute an established geriatric principle,[8] they are not necessarily equated with better care. Moreover, some physicians and clinics may be more efficient than others. Standard appointment lengths also do not prevent a practitioner from spending more time with an individual patient. However, keeping "on schedule" then depends on having other patients who take less than the allotted time. Seeing several frail or complex elderly patients in succession may put pressure on a physician to hasten through other patient visits, thereby increasing the risk of overlooking critical information or physical findings. This theoretic threat to quality of care becomes important in light of the federal government's promotion of prepaid health plans for Medicare recipients as a way of holding down Medicare costs.[36]

In conclusion, the results of our survey of 127 licensed primary care clinics in California suggest that the geriatric

principles of functional assessment and interdisciplinary evaluation have been entering everyday clinical practice. Despite the growing number of very old and frail patients in primary care practices, however, 30% of teaching clinics and 58% of nonteaching clinics lacked physicians with an interest in geriatric medicine. This raises concern that many physician trainees may not be receiving adequate exposure to geriatric knowledge and principles of clinical care. Also of concern is the finding that most clinics do not routinely provide house calls to their homebound older patients, who may have difficulty getting to the clinic. The finding that CME in geriatrics is independently associated with the performance of both functional and interdisciplinary assessment supports the argument that medical societies and schools should increase the number and availability of such courses for primary care physicians. Because of the relatively high acceptance rate of Medicare assignment and the frequent availability of social services, medical clinics may be an attractive option for older persons. Clinics that encourage a rapid turnover of patients by means of short appointments, however, may not be in the best interest of a complex, frail patient. Although based on a small sample of clinic-based HMOs, our findings suggest that HMOs have shorter average appointments than fee-for-service and VA clinics and that HMO physicians have less flexibility in adjusting appointment lengths to meet their patients' needs. Further research is needed to analyze geriatric primary care in the prepaid and fee-for-service settings.

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Conferences and Reviews

Clues in Diagnosing Congenital Heart Disease

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A number of practical office and bedside clues to cardiac disease in infants and children have been passed on through the years. They relate to the history, to the inspection and palpation components of the physical examination, and to knowledge of the specific cardiac defects that are likely to be associated with certain clinical syndromes. With the possible exception of coarctation of the aorta, the clues are not diagnostically specific. In many instances, however, they serve to narrow a broad array of diagnostic possibilities to 2 or 3 and, with the aid of other clues and auscultation, they can often be distinguished from one another. When a primary care physician is confronted with a child who has an incidental murmur that is "probably" innocent but could be organic, useful clues favoring an organic murmur are a history of congenital heart disease in a first-degree relative; a history of maternal rubella syndrome, alcohol use, or teratogenic drug use during pregnancy; a history of inappropriate sweating; a history of syncope, chest pain, or squatting; maternal diabetes mellitus; premature birth; birth at a high altitude; cyanosis; abnormal pulsations; recurrent bronchiolitis or pneumonia; chronic unexplained hoarseness; asymmetric facies with crying; and a physical appearance suggestive of a clinical syndrome.

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Primary care physicians are in the forefront of providing health care and are often the first to see a patient with congenital heart disease. When heart disease is obvious, the decision is an easy one: the patient is referred to a cardiologist. It is when a murmur is discovered incidentally that a judgment must be made as to whether the murmur is organic or innocent. Echocardiography is a highly specialized procedure and must be recorded by a technician who is cognizant of congenital heart defects. Moreover, it is not to be used merely to rule out congenital heart disease. Primary physicians must therefore continue to rely for diagnosis on the history and physical examination findings and perhaps on the x-ray film and electrocardiogram.

When a physician is confronted with a child who has an incidental murmur that is "probably" innocent, a number of clues may be helpful. My review focuses on these clues, with the aim of providing primary care physicians with information that may be useful in differentiating organic from innocent murmurs.*

These clues are documented in the earlier literature, and they have retained their value despite ever-expanding technologic advances in cardiology. When elicited, their presence tips the scales in favor of an organic murmur, and consultation with a cardiologist should be considered. The clues relate to history, to inspection, and to palpation. They are scattered over decades in the cardiology literature and thus are not readily available to primary physicians. They can sometimes even help lead to a reasonably accurate presumptive diagnosis that, although not essential at the level of primary care, is a great source of pride and pleasure and may also be of some help to the patient.

Murmurs of specific lesions are not always those classically described. The murmur of atrial septal defect, even when classic, can easily be confused with an innocent murmur. The murmur of ventricular septal defect may be soft, and that of patent ductus arteriosus is typically but not necessarily loud and continuous. In tetralogy of Fallot, cyanosis together with a systolic ejection murmur maximal at the second or third left interspace is highly suggestive. With all of these conditions, the murmur can be soft and sound surprisingly benign.

*See also "Congenital Heart Disease—The First Test," by A. R. Hohn on pages 435-436 of this issue.

Clues Related to History

Family History

The presence of a congenital heart lesion in a first-degree relative can have considerable diagnostic relevance.[1-10] Not only can congenital heart disease run in families, but the specific lesion in first-degree relatives is often concordant. According to Nora, the recurrence rate in a first-degree relative is 1% to 4%.[7] If there are two affected first-degree relatives, the recurrence rate is 3% to 12%. The lesions most likely to recur are ventricular septal defect, patent ductus arteriosus, atrial septal defect, and tetralogy of Fallot. These lesions should be high on the list of differential diagnoses in a patient with a positive family history.

Idiopathic hypertrophic subaortic stenosis is in a class by itself.[9,10] The stenosis is due to a hypertrophic cardiomyopathy of unknown origin that tends to obstruct outflow from the left ventricle during systole. On auscultation, there is only a soft systolic murmur at the left sternal border or at the apex, and in the early stages of the disease there may be no murmur at all. When present it can easily be confused with an innocent murmur. The incidence of the disease in a first-degree relative is, according to Maron,[9] as high as 20%, making it mandatory to screen family members by echocardiography not only when a relative is affected but also when there is a history of sudden unexplained death.

Maternal and Perinatal History

The maternal history also can be an important clue to diagnosis. Infants born of women with diabetes mellitus can have a wide variety of cardiac defects.[11,12] Chief among these is a transient cardiomyopathy that is present at birth and is demonstrable by echocardiography.[13-17] The abnormality

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consists of a form of subaortic stenosis with ventricular septal hypertrophy similar to idiopathic hypertrophic subaortic stenosis.[15-17] It has been reported in 30% of these infants, in many of whom congestive heart failure develops.[18] The condition requires prompt recognition and treatment because it can be life threatening. The cause of this abnormality has not been clearly elucidated, but it may be related to either fetal hyperglycemia or fetal hyperinsulinemia. In a symptomatic infant, the symptoms begin to resolve in 2 to 4 weeks, and the hypertrophy resolves in 2 to 12 months.[14]

Other cardiac defects also occur with greater frequency in infants of diabetic women. According to one study, the incidence of congenital heart disease is 4%, which is five times the incidence in the general population.[13] The defects cover a broad range, but transposition of the great arteries is the prevalent lesion.[11,12] Thus, any child of a diabetic woman who is noted in the neonatal nursery to have cardiac cyanosis should be considered to have transposition.

Three situations in which the history can be of diagnostic importance are in rubella syndrome babies, premature infants, and children who were born and lived at high altitudes. In all three cases, patent ductus arteriosus is possible.

This is the most frequent cardiac anomaly in rubella syndrome babies,[19] often in association with pulmonary artery stenosis.[20,21] The stenosis usually involves the branch pulmonary arteries. The frequency of patent ductus arteriosus with pulmonary artery stenosis may be as high as that of patent ductus arteriosus alone. The pulmonary artery stenosis is usually mild or moderate, however, and is often not detected by clinical examination.

Delayed closure of the ductus arteriosus in premature infants is common.[22-28] The incidence is high in infants with low birth weights, particularly in those under 1,000 grams at birth and in those with pulmonary disease.[27,29,30] The delayed closure is the result of a failure of the ductus to respond to the vasoconstrictor effect of oxygen and to the dilator effect of prostaglandin E_2.[31,32]

Patent ductus arteriosus is extremely common in children born and living at high altitudes, and the anomaly can persist when the patient emigrates to sea level.[33-35] Although patent ductus arteriosus accounts for only 5% or 10% of all cardiac anomalies,[36,37] at high altitudes such as Mexico City it is the most frequent congenital heart defect, and in the Peruvian Andes (altitude 4,500 to 5,000 m) the incidence is 30 times that at sea level. In fact, it is more frequent in the Peruvian Andes than coronary artery disease.[33-35] The cause for persistent patency of the ductus arteriosus at high altitudes is hypoxemia and pulmonary hypertension, both of which remain as chronic conditions after birth.

A history of maternal exposure to alcohol or drugs[38-41] may be difficult to elicit but when revealed, it provides a clue that may be important to diagnosis. In the case of alcoholism, a syndrome results that is clinically recognizable and is discussed in the clinical syndrome section.

A wide variety of drugs, both recreational and medicinal, may cause malformations that include cardiovascular disease in the offspring. The exact frequency is unknown because of differences in methods and in reporting. A history of maternal epilepsy is particularly important because of the relatively common fetal hydantoin syndrome. This condition also will be discussed in the segment devoted to syndromes. Until more information becomes available, the use of any drug considered teratogenic, whether it is known to cause congenital heart disease or not, should favor the diagnosis of an organic murmur over a murmur that is "probably" innocent.

Patient History

A history of diaphoresis is an important clue in diagnosing heart disease. Some children with congenital heart disease sweat more than those without heart disease.[42-45] Inappropriate sweating has been found to be prevalent in children with large left-to-right shunts at the ventricular and atrial levels. Moreover, increased sweating occurs in children who are in borderline or mild heart failure.[45]

Today it is generally accepted that inappropriate sweating in an infant, particularly while feeding, is a reliable sign of overt or impending heart failure. This observation has no diagnostic specificity, but it does categorize the lesion as one of the defects that tend to cause heart failure, and, together with other clues, it may help in diagnosis. The mechanism of this phenomenon remains unclear.

Syncope of cardiac origin is relatively rare in infants and children. When it does occur, it is almost always due to an arrhythmia that is sufficiently prolonged, rapid, or disorganized to compromise cardiac output. But there is one congenital cardiac lesion, aortic stenosis, that can be associated with syncope and, in some cases, with sudden death.[46] Sudden death in patients with severe aortic stenosis is a feared complication regardless of the age of the patient.[47-53] Syncope arising from this lesion is extremely rare in childhood.

Chest pain is not nearly as common in children as in adults, and, when present, it is rarely associated with congenital heart disease. But as with syncope, the one lesion that must be excluded is aortic stenosis.[53-55(p978)] The character of the pain need not be typical of coronary artery insufficiency. It may last for only a few minutes or for hours. It may or may not radiate to the arms, face, or neck. To compound the problem of diagnosis, a precise and detailed description often cannot be obtained from a child. Although the pain is usually induced by effort, it can occur at rest. Other congenital cardiac causes of chest pain include severe pulmonic stenosis, mitral valve prolapse, and primary pulmonary hypertension.[55,56]

A history of squatting should immediately bring to mind tetralogy of Fallot because many of these patients squat following exertion. Characteristically, the children flex their knees and lean slightly forward on their legs from a sitting position. They may run for a short distance and, when they become fatigued, suddenly squat down. Infants who cannot squat often assume the knee-to-chest position when they become fatigued.

After exercise, venous return from the lower extremities is extremely low in oxygen saturation. With squatting, venous return from the lower extremities is impeded, and, as a result, the oxygen saturation of mixed systemic venous return rises.[57-60] O'Donnell and McIlroy contend that squatting does not kink the arteries and veins in the legs but rather, brings the heart closer to the level of the feet, thereby increasing central blood volume, blood pressure, and cardiac output.[61]

Clues From the Physical Examination

Cyanosis

There are two major categories of cyanosis, and it is important to distinguish them from each other. Peripheral cyanosis is of no clinical importance and is not to be confused

with central cyanosis. Peripheral cyanosis involves the lips, fingers, and toes and occurs with chilling, fright, anxiety, illness, or fatigue; it is often a source of concern to parents. The identifying feature is that it does not involve the mucosa of the lips, whereas central cyanosis, which originates from the lungs or the heart, does.

The cardinal feature of pulmonary cyanosis is that it disappears or greatly diminishes after oxygen is administered and also with crying if there is not extensive intrapulmonary shunting. The act of crying produces deeper inspiratory efforts that open more alveoli and may increase the quantity of oxygen delivered to them.

Cardiac cyanosis is not relieved with oxygen and tends to worsen with crying because the thoracic and cardiac pressure alterations intensify the shunting of venous blood into the arterial circuit. When cardiac cyanosis is observed in a newborn, transposition of the great arteries is the most likely diagnosis. There may be only a soft systolic murmur or no murmur at all. Whether a murmur is audible or not, cardiac cyanosis at any age requires consultation on an urgent basis because lesions such as transposition and pulmonary atresia demand early evaluation and treatment.

Cyanosis is clinically detectable when arterial saturation is less than 80% to 85% unless the patient has anemia. Cyanosis is a helpful clue because it places the defect within the cyanotic group of heart diseases, which includes tetralogy of Fallot, transposition of the great arteries, pulmonary atresia, tricuspid atresia, truncus arteriosus, and various complex cardiac abnormalities. Of these, tetralogy of Fallot and transposition are by far the most common.

The age of the patient can help to further narrow the differential diagnosis. For example, unless treated surgically, infants with transposition rarely survive the first year of life. Without treatment, about 30% die in the first week of life, 50% in the first month, 70% within six months, and 90% in the first year.[62] On the other hand, 75% of untreated patients with tetralogy of Fallot (without pulmonary atresia) can be expected to survive the first year, 60% the first three years, and 30% at ten years.[63] Thus, when a cyanotic child is beyond the early months of life, the statistical odds favor a diagnosis of tetralogy over transposition merely by the fact that the patient is still alive and, the greater the age, the better the odds.

Similarly, the age at which cyanosis is first observed has important diagnostic implications. Levin and colleagues noted that cyanosis was observed during the first hour of life in 54% of infants with transposition and during the first day in 89%.[64] With tetralogy of Fallot, although cyanosis can be obvious on the first day of life, it may be delayed for weeks or even months.[65(p193),66(p456)] According to Rowe and Mehrizi, cyanosis of some degree is present from birth in only half of patients with tetralogy.[65] These data support the current recommendation that cardiac cyanosis in a neonate must be considered due to transposition of the great arteries until proved otherwise.

Differential cyanosis affecting the feet but not the hands is a rare event, but it has diagnostic importance. To perceive this, it may be necessary to inspect the fingers while they are positioned alongside the toes. The phenomenon may be present in patients with complete interruption of the aortic arch[67] or patent ductus arteriosus with associated coarctation of the aorta or with associated increased pulmonary vascular resistance.[55(p33)] In all three conditions, desaturated blood enters the descending aorta by way of the ductus arteriosus.

There is a unique clue to inapparent cyanosis that deserves mention—the bright red tips of the fingers and toes ("tuft" erythema). This phenomenon reflects a mild degree of desaturation that is only episodically lowered to the visible level of 80% to 85%. Nadas suggested that in these patients the arterial oxygen saturation is about 90%.[68(p11)] This manifestation is considered to be the precursor of visible cyanosis and clubbing and is sometimes seen in patients with left-to-right shunts and increasing pulmonary vascular obstruction, as in ventricular septal defects.

Pulsations

Visible or palpable pulsations sometimes provide a helpful clue to diagnosis.* Visible pulsations in the suprasternal notch can occur with exercise, apprehension, anxiety, or fever. They can also occur with aortic stenosis, aortic insufficiency, coarctation of the aorta, and patent ductus arteriosus. These lesions must be suspected when it has been determined that apprehension, anxiety, and fever are not the basis.

Best known for its diagnostic specificity is absent or diminished pulsations in the lower extremities, the hallmark of coarctation of the aorta. One caveat is worthy of mention: Although the pulse needs to be palpated in only one lower extremity, it is mandatory to do so in both upper extremities because there may be congenital stenosis of one of the subclavian arteries. Also, if the site of constriction is above the origin of the left subclavian artery, the pulse will be normal in the right arm but diminished or absent in the left arm; if it is below the left subclavian artery and if the right subclavian artery arises aberrantly from a site below the coarcted segment, as it sometimes does, the pulse will be affected in only the right arm.[71(pp406,407)] Whenever possible, information gained from the pulses should be confirmed by a blood pressure measurement. The soft murmur of coarctation can easily be dismissed as an innocent murmur if the physician fails to listen in the interscapular area or fails to palpate the peripheral pulses.

Palpable hepatic pulsations are very rare, but, when present, they suggest that the defect is pulmonic stenosis (with tricuspid insufficiency) or tricuspid atresia, although hepatic pulsations may also be present in a patient with a hypoplastic right ventricle or in primary pulmonary hypertension. The pulsations are appreciated by palpation but usually not by inspection.

Age of Onset of Murmurs

The age at which a murmur first appears can be helpful in diagnosis. This assumes, of course, that a heart murmur was not previously overlooked, either by the examiner or by others. Murmurs detectable at birth usually represent aortic or pulmonic stenosis, either isolated or in combination with other lesions. The turbulence in these lesions arises from obstruction to ventricular outflow and is present even when pulmonary vascular resistance is high. Other less common causes include congenital tricuspid insufficiency and underdevelopment of the left side of the heart.[72] The murmur in all of these conditions is systolic in time.

The murmur of a patent ductus arteriosus may occur as early as 6 hours of age. It is maximal at the second left interspace and is continuous, abbreviated continuous, or

*References 55, 65 (p 46), 69 (pp 85, 86), 70.

purely systolic. It need not be loud and can easily be confused with an innocent murmur if it is limited to systole.

The murmur of a ventricular septal defect is not usually audible at birth. It may be delayed for several hours to a few weeks. The appearance time depends not only on the size of the defect but also on the level of pulmonary vascular resistance. Pulmonary vascular resistance is normally elevated at birth, so little or no shunting occurs.[73,74] It may take several days for the resistance to drop to a level at which significant shunting occurs and a murmur develops.

The murmur of an atrial septal defect does not appear until later because of reduced compliance of the right ventricle in the neonate. The murmur is only rarely audible in the neonatal period, and it may not be detectable for a year or more after birth.

Age of Onset of Heart Failure

Cardiac failure due to a congenital cardiovascular defect occurs mainly during infancy.[72,75-83] At a given age, certain defects predominate. Thus, the age when heart failure begins is a helpful clue to diagnosis. It is not diagnostically specific, but it does narrow the range of possibilities. The most common lesions at a specific age period are as follows:

- Birth to 1 week: hypoplastic left heart, transposition of the great vessels, coarctation of the aorta, and patent ductus arteriosus;
- 1 week to 2 months: coarctation of the aorta and transposition of the great vessels;
- Beyond 2 months: ventricular septal defect.

Some years ago Rudolph, reporting an observation that has since had an important bearing on the early recognition of congenital heart disease, pointed out that infants with cardiac lesions that burden the left ventricle can have episodes of respiratory distress without other evidence of heart failure.[84] The history often suggests bronchiolitis, asthma, or pneumonia. These patients are frequently misdiagnosed because the noisy breathing may obscure a cardiac murmur, or there may not be a murmur at all with defects such as coarctation of the aorta or cardiomyopathy. Rudolph stated that "It has been estimated that of all infants admitted to the hospital, in whom a diagnosis of cardiac failure is made, a relatively large proportion (one-quarter to one-third) have been treated for respiratory infections without recognition of the heart disease."[84(p1000)]

Clinical Syndromes As Clues

Cardiac defects are associated with a great number of clinically recognizable syndromes.[85-130(p120)] Although any defect can be a part of any syndrome, specific defects predominate in some, and this knowledge provides a helpful clue to cardiac diagnosis (Table 1).[126] A description of the syndromes can be found in most standard pediatric textbooks. There are, however, some syndromes that deserve elaboration either because they are particularly common—Down, Turner's, Noonan's, fetal alcohol, or fetal hydantoin—or because the cardiac defect is the dominant feature and may not be appreciated by noncardiologists, such as cardiofacial, cardiovocal, and Williams.

Down Syndrome

Down syndrome (trisomy 21) occurs in 1 of 660 live births, with 40% to 50% born with some kind of cardiac defect, clearly making it the most common syndrome associated with congenital heart disease.[85-87,126] The wide variety of cardiac defects includes the endocardial cushion defect, ventricular septal defect, atrial septal defect, tetralogy of Fallot, and isolated patent ductus arteriosus. The endocardial cushion defect and ventricular septal defect are by far the most common, and, until proved otherwise, these should head the list of differential diagnoses. Even if a heart murmur is not present, physicians must maintain a high index of suspicion. In some newborn nurseries, it is routine to do an electrocardiogram or echocardiogram on babies with Down syndrome even in the absence of a murmur. If the electrocardiogram shows left axis deviation (or an indeterminate axis) with a counterclockwise loop, this is strong evidence of an endocardial cushion defect.

TABLE 1.—*Syndromes With Congenital Heart Disease**

Syndrome	*Dominant Cardiac Defect*
Down	Endocardial cushion defect, ventricular septal defect
Trisomy D	Ventricular septal defect, patent ductus arteriosus
Trisomy E	Ventricular septal defect, patent ductus arteriosus
Wolf	Atrial septal defect, ventricular septal defect
Turner's	Coarctation of the aorta, aortic stenosis
Fetal alcohol	Ventricular septal defect, atrial septal defect, tetralogy of Fallot
Ellis-van Creveld	Single atrium
Laurence-Moon-Biedl	Tetralogy of Fallot, ventricular septal defect
Carpenter's	Patent ductus arteriosus, ventricular septal defect
Holt-Oram	Atrial or ventricular septal defect
Fanconi's	Patent ductus arteriosus, ventricular septal defect
Thrombocytopenia-absent radius	Atrial septal defect, tetralogy of Fallot
Rubinstein-Taybi	Patent ductus arteriosus
Noonan's	Pulmonic stenosis, atrial septal defect
DiGeorge	Tetralogy of Fallot, right aortic arch
Smith-Lemli-Opitz	Ventricular septal defect, patent ductus arteriosus
De Lange's	Tetralogy of Fallot, ventricular septal defect
Goldenhar's	Tetralogy of Fallot
Williams	Supravalvular aortic stenosis, peripheral pulmonic stenosis
Multiple lentigenes (leopard)	Pulmonic stenosis

*From Noonan.[126]

Turner's and Noonan's Syndromes

Turner's syndrome occurs in girls with an XO chromosome pattern and with gonadal dysgenesis, whereas a syndrome with similar clinical features, Noonan's syndrome, occurs in both boys and girls with normal chromosome patterns.[88-97] In both syndromes, short stature and webbing of the neck are cardinal features. Also, both syndromes are often associated with congenital heart disease. The heart is affected in about 30% of children who have Turner's syndrome, coarctation of the aorta being the predominant lesion. A bicuspid aortic valve is often associated with coarctation but also occurs as an isolated lesion. In Noonan's syndrome, the most common cardiac lesion is pulmonic stenosis.

Fetal Alcohol Syndrome

The fetal alcohol syndrome has been the subject of increasing attention during the past decade. It occurs in the offspring of alcoholic women and is characterized by growth retardation, developmental delay, and typical facies.[38,39,126] The facial stigmata include short palpebral fissures, relative maxillary hypoplasia, and microcephaly. Of these patients, 30% to 40% have associated congenital heart disease, with ventricular septal defect, atrial septal defect, and tetralogy of Fallot being the chief disorders.

Fetal Hydantoin Syndrome

The fetal hydantoin syndrome has recently received a good deal of attention.[39,40] A history of analeptic drug use during pregnancy is important because about 10% of infants who have exposure to hydantoin prenatally have the features of this syndrome. The characteristics include hypertelorism, broad depressed nasal bridge, cupid's bow of the upper lip, cleft lip or palate, hirsutism, and distal phalangeal and nail hypoplasia. There is an increased risk of congenital heart disease, but no specific lesion appears to predominate.

Williams Syndrome

Patients with the Williams syndrome have elfin facies, often with abnormal teeth, a hoarse voice, growth retardation, and mental retardation.[126] In some, an association with hypercalcemia during infancy has been shown. Congenital heart disease is an integral part of the syndrome, with supravalvular aortic stenosis being the usual lesion. It is often associated with peripheral pulmonic stenosis.

The phenotypic characteristics of this syndrome are not present at birth and may be delayed months or even years. It is rare that the syndrome is clinically recognizable before 9 months of age.

Cardiovocal Syndrome

The cardiovocal syndrome should be suspected in any child with a heart murmur and chronic hoarseness.[113] The hoarseness is due to secondary paralysis of the laryngeal nerve, usually the left, and is a relatively late manifestation. It occurs in patients with large left-to-right shunts with pulmonary hypertension.

The cause of the hoarseness is attributed to a large tense pulmonary artery that compresses the left recurrent laryngeal nerve against the aorta and trachea. Because hoarseness is a late manifestation, this syndrome is not usually recognized until heart failure develops. Heading the list of differential diagnoses are patent ductus arteriosus, ventricular septal defect, and atrial septal defect.

Cardiofacial Syndrome (Asymmetric Crying Facies)

The cardiofacial syndrome is characterized by lower facial asymmetry with crying.[126-130] It is a subtle sign and can be easily overlooked. Its importance is its association with congenital heart disease as well as with other malformations. According to Cayler, 5% to 10% of babies with congenital heart disease have evidence of lower facial weakness.[128] Although a variety of cardiac lesions may be involved, ventricular septal defect should be suspected.

Innocent Murmurs

Innocent murmurs are by far the most common in infants and children and thus deserve some mention. In the absence of the aforementioned clues, examiners must consider the real possibility of an innocent murmur when there is no other evidence of cardiac disease. There are four common innocent murmurs: innocent murmur of the newborn, vibratory murmur (Still's or musical murmur), the venous hum, and the innocent pulmonic ejection murmur. The first three can usually be identified with confidence by their characteristic features. Because I have recently discussed innocent murmurs in detail elsewhere,[131(pp481-483)] they will be only briefly presented here.

Innocent Murmur of Newborns

The innocent murmur of newborns is a short systolic ejection murmur that is usually of grade II or III intensity. It is present at birth but usually disappears by 3 months of age. The identifying feature is that it is clearly transmitted to both axillae. The murmur is caused by turbulence in the peripheral pulmonary arteries because of their disproportionately small size. In these infants, there is, in fact, stenosis of the peripheral arteries and thus the popular term, "peripheral pulmonary artery stenosis of the newborn." The condition resolves itself in the early months of life.

Vibratory Murmur

The vibratory murmur is a systolic murmur, usually of grade II (rarely grade III) intensity, located in the midprecordium or toward the apex. It is most often heard in children between the ages of 2 and 7 years. The salient feature is a twanging sound, thus the common term, "fiddle-string or twanging string murmur." The murmur is thought to be due to turbulence in the outflow tract of the left ventricle. It tends to lessen or even disappear completely when the patient assumes an upright position.

Venous Hum

The venous hum is a murmur, usually of grade II or III intensity, that occupies both systole and diastole. It is most often heard in the right upper sternal area but can sometimes be heard on the left, in which case it is easily confused with a patent ductus arteriosus. The identifying features are that it is louder when the patient is upright and disappears when the patient's neck vessels on the respective side are compressed. The murmur is due to turbulence in the great veins of the neck and thus disappears when these are compressed. Accentuation when the patient is upright is due to the added effect of gravity on flow into the right atrium.

Innocent Pulmonic Ejection Murmur

The innocent pulmonic ejection murmur is systolic in time, ejection in character, and usually of grade II intensity. It

is limited to the left upper sternal area and is identical to the murmur of an atrial septal defect and mild pulmonary stenosis. In all three, the murmur is due to turbulence in the outflow tract of the right ventricle. With the innocent murmur, turbulence is the result of increased cardiac output. It is therefore important to reexamine the patient when causes of increased cardiac output such as fever, apprehension, or exercise are eliminated.

Summary

Primary physicians are often faced with a situation in which a cardiac murmur is discovered incidentally, and a decision must then be made as to whether it is innocent or organic. In this review, clinical clues are presented that are helpful in making this distinction.

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Pheochromocytoma

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The sympathochromaffin (sympathoadrenal) system consists of two components[1,2]: the sympathetic nervous system and the chromaffin tissues including the adrenal medullae. The principal endocrine, neurotransmitter, paracrine, and autocrine products of the sympathochromaffin system are the catecholamines—epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine. The vast majority of sympathetic postganglionic neurons release norepinephrine; some release acetylcholine, the other classic neurotransmitter. Most of the chromaffin cells of the adrenal medullae secrete epinephrine; some secrete norepinephrine. Thus, although the adrenal medullae can be conceptualized as sympathetic postganglionic neurons without axons,[2,3] the predominant catecholamine released by the two components of the sympathochromaffin system differs.

Cells of the sympathochromaffin system also produce an array of peptides of potential biologic importance. A partial list includes neuropeptide Y, vasoactive intestinal peptide, galanin, somatostatin, growth hormone-releasing hormone, calcitonin, proopiomelanocortin derivatives including corticotropin, insulinlike growth factor II, vasopressin, and oxytocin. Their pathophysiologic roles, if any, are generally unknown, but Cushing's syndrome due to the ectopic secretion of corticotropin from a pheochromocytoma has been recognized.

There are three well-established clinical disorders of the sympathochromaffin system.[2] Two are catecholamine-deficiency states. Sympathetic neural failure (norepinephrine deficiency) results in postural (orthostatic) hypotension, a sharp decrease in blood pressure that typically causes cerebral hypoperfusion when a person stands. Adrenomedullary failure (epinephrine deficiency) generally does not produce clinical manifestations. When associated with glucagon deficiency, however, it can result in hypoglycemia. This last has been well documented only in a subset of patients with insulin-dependent diabetes mellitus. Because insulin-dependent diabetes is a common disease, however, defective glucose counterregulation attributable to combined deficiencies of the glucagon and epinephrine secretory responses to a falling plasma glucose concentration[4] is the most common clinical disorder of the sympathochromaffin system.

Catecholamine excess commonly results in hypertension along with typical symptoms. Catecholamine overproduction from pheochromocytomas—tumors arising from chromaffin cells—is an uncommon but often curable cause of hypertension. Related tumors, such as neuroblastomas and ganglioneuromas, produce catecholamines but rarely release these in sufficient quantities to produce clinical manifestations. Rather, the catecholamines are degraded within the tumors, and large quantities of catecholamine metabolites appear in the plasma and urine. Pheochromocytoma is the topic of this review.* This subject has been reviewed elsewhere.[2,5-8]

Physiology of the Sympathochromaffin System

Catecholamine Biosynthesis and Degradation

Catecholamines are compounds with a dihydroxyphenyl ("catechol") ring structure and an amine side chain. The naturally occurring catecholamines are dopamine, norepinephrine, and epinephrine (Figure 1). They are synthesized, stored in, and released from sympathetic postganglionic neurons and chromaffin cells, including those that compose the adrenal medullae.

The catecholamines are synthesized (Figure 1) from the amino acid tyrosine, which is derived from the diet or formed by hydroxylation of the essential amino acid phenylalanine. Tyrosine hydroxylase, the enzyme that converts tyrosine to dihydroxyphenylalanine (dopa), is the rate-limiting enzyme in catecholamine biosynthesis. Its activity is product inhibited, and it is induced by increased preganglionic neural firing. In the presence of a nonspecific decarboxylase, dopa is converted to dopamine, which is the final product of catecholamine biosynthesis in some systems, such as interneurons in the sympathetic ganglia. After transport into cytoplasmic vesicles (storage granules), dopamine can be converted to norepinephrine in the presence of dopamine β-hydroxylase. Norepinephrine is the final catecholamine product of sympathetic postganglionic neurons. Other tissues, such as the adrenal medullae, have chromaffin cells that express phenylethanolamine-*N*-methyltransferase, the enzyme that converts norepinephrine to epinephrine, the final catecholamine product of those cells.

Interestingly, phenylethanolamine-*N*-methyltransferase is a cytoplasmic enzyme. Thus, norepinephrine must be transferred to the cytoplasm to be methylated to form epinephrine, which then reenters the granules. In addition, the enzyme is inducible by glucocorticoids. Given portal venous flow from the adrenal cortex to the medulla, this might explain the persistence of epinephrine-secreting chromaffin cells in the adrenal medullae.

Catecholamines are stored in cytoplasmic granules along with adenosine triphosphate and various proteins including dopamine β-hydroxylase and chromogranin A. When stimulated, the postganglionic elements (neurons and chromaffin

*See also "Pheo or Not a Pheo, That Is the Question," by Sheldon G. Sheps, MD, pages 433-435 of this issue.

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ABBREVIATIONS USED IN TEXT

COMT = catechol-*O*-methyltransferase
CT = computed tomography
cyclic AMP = adenosine 3′,5′-cyclic phosphate
HPLC = high-pressure liquid chromatography
MAO = monoamine oxidase
MEN = multiple endocrine neoplasia
MIBG = *m*-iodobenzylguanidine
MRI = magnetic resonance imaging
VMA = vanillylmandelic acid

cells) release the entire soluble contents of the granules by exocytosis. Thus, proteins such as chromogranin A, as well as catecholamines, are released into the extracellular fluid.

Catecholamines are degraded by two principal enzyme systems, catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO) (Figure 1). Catechol-*O*-methyltransferase converts norepinephrine and epinephrine to their respective *O*-methyl metabolites, normetanephrine and metanephrine, which are often referred to as the total metanephrines. Monoamine oxidase converts norepinephrine and epinephrine to dihydroxymandelic acid. Through a series of reactions, detailed elsewhere,[2,9] these intermediates, the metanephrines and dihydroxymandelic acid, can ultimately form products that serve as substrates for MAO and COMT, respectively, resulting in their conversion to the major end product of extra central nervous system catecholamine metabolism, vanillylmandelic acid (VMA). One intermediate that is also produced in substantial quantities, and is sometimes measured, is methoxyhydroxyphenylglycol. Dopamine metabolism (not shown in Figure 1) by MAO and COMT leads to the formation of homovanillic acid, which differs from VMA only by the absence of a hydroxyl group on the β-carbon of the side chain.

In general, catecholamines in the sympathochromaffin cells are degraded by MAO, whereas released catecholamines are largely degraded by COMT. Released catecholamines are also conjugated, largely to the sulfate in humans, and this may be another important route of inactivation. In plasma, 60% to 80% of the total epinephrine and norepinephrine and virtually all of the dopamine, and roughly half of the catecholamines in urine, are conjugated. Like other metabolites, these conjugates are not measured with now standard methods for measuring catecholamine levels in plasma and urine.

Catecholamines are cleared rapidly from the circulation. Plasma half-times are one to two minutes. Clearance is largely extrarenal; less than 5% appears in the urine. The kidneys and particularly the liver are major clearance sites, but catecholamines are extracted by most body tissues. Thus, arterial epinephrine concentrations are roughly twice those measured in antecubital venous blood. Arteriovenous differences for norepinephrine are often small, even immeasurable. This is deceptive, however. About 50% of norepinephrine is extracted across the forearm, but (unlike

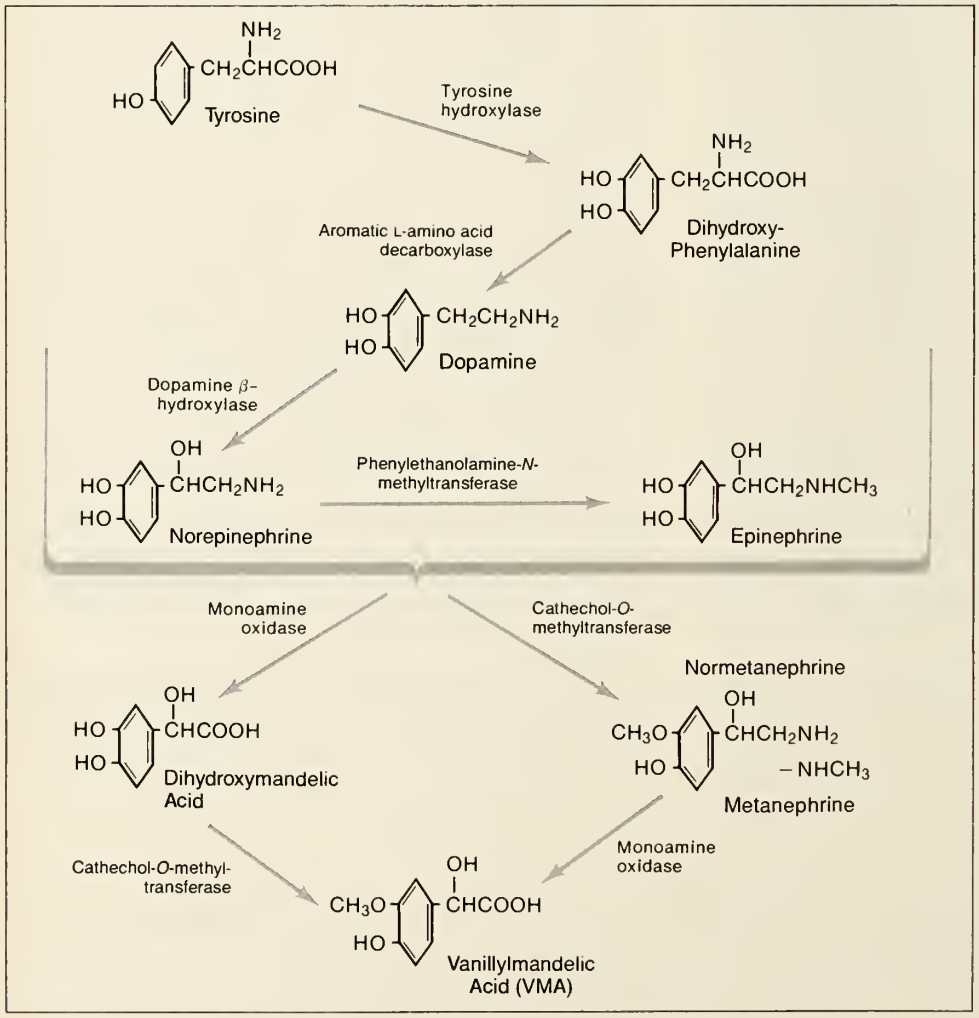

Figure 1.—Catecholamine biosynthesis and metabolic degradation are shown.

epinephrine) a similar amount is released from sympathetic postganglionic neurons.

Biologic Roles of the Catecholamines

Epinephrine, norepinephrine, and dopamine are neurotransmitters in the central nervous system. Outside of the central nervous system, epinephrine is a hormone of the adrenal medullae, and norepinephrine is primarily a neurotransmitter of sympathetic postganglionic neurons. Dopamine is probably also a neurotransmitter, although its physiologic role has not been defined clearly.

Neurally regulated secretion of epinephrine from extra-adrenal chromaffin tissues (not sympathetic neurons) occurs, but in the absence of the adrenal medullae even stimulated plasma epinephrine levels are not high enough to produce measurable biologic effects.[1,10] Therefore, the biologic actions of epinephrine released from extra-adrenal sites, if any, must be autocrine or paracrine (including neurotransmitter) rather than hormonal, at least in adults. Thus, epinephrine functions primarily as a hormone of the adrenal medullae, and its plasma concentration is a valid index of its secretion.

In contrast to epinephrine, most norepinephrine is released from axon terminals of sympathetic postganglionic neurons in direct relation to adrenergic receptors on innervated target cells. Transport through the circulation is not required to explain its biologic actions. Most (80% to 90%) of the released norepinephrine is dissipated locally by reuptake into the axon terminal (uptake 1), where it is either stored in vesicles or metabolized, or by uptake into other cells adjacent to the synaptic cleft (uptake 2), where it is metabolized. Thus, only a small fraction escapes into the circulation. Nonetheless, the plasma norepinephrine concentration is a reasonable index of sympathetic neural activity under common physiologic conditions, at least in the basal state and during upright activity in humans.[1,2] Under some conditions, however, such as hypoglycemia, substantial amounts of norepinephrine (along with large amounts of epinephrine) are released from the adrenal medullae. Under such conditions, the plasma norepinephrine concentration is not an index of sympathetic neural activity per se but of sympathochromaffin activity. During vigorous physical activity and in a variety of pathophysiologic states, such as during a surgical procedure, acute myocardial infarction, and diabetic ketoacidosis, circulating norepinephrine is probably derived from both the sympathetic nerves and the adrenal medullae, and its concentrations can be high enough to produce measurable effects. Under these conditions, norepinephrine may function as a hormone as well as a neurotransmitter.

This physiology is relevant to the diagnostic use of plasma catecholamine measurements. Norepinephrine released from sympathetic neurons in amounts sufficient to produce biologically active norepinephrine concentrations in the synaptic clefts can be associated with very small, even undetectable, increments in its plasma concentration.[1] Because most of the released norepinephrine is dissipated locally, there is a steep concentration gradient from the cleft to the plasma when the system is activated. On the other hand, if norepinephrine is released directly into the circulation (as from a pheochromocytoma), substantial increments in its plasma concentration are required to produce biologically active synaptic cleft concentrations.[2] Thus, normal (or even somewhat elevated) plasma norepinephrine concentrations in a patient who is hypertensive at the time a specimen is obtained provide good evidence that the hypertension is not the result of a pheochromocytoma.

Biologic Actions of the Catecholamines

Catecholamines produce a variety of hemodynamic and metabolic effects. These are the result of catecholamine occupancy of adrenergic receptors (adrenoceptors) on the surface of target cells and a consequent series of intramembrane and intracellular biochemical events. Adrenergic receptors have been divided into α- and β-adrenergic receptor types and α_1-, α_2-, β_1-, and β_2-adrenergic receptor subtypes. The subtypes are determined by measuring responses to various agonists and antagonists in vivo and in vitro and the binding of ligands (generally antagonists) and competition for binding of these ligands by agonists and antagonists in vitro. Their primary structures have been recently deduced, and their orientation in the plasma membrane inferred, from the cloned genes.[11] Indeed, the latter approach has led to the discovery of a new β_3-adrenergic receptor[12] and a new α_{2B}-adrenergic receptor.[13]

β-Adrenergic receptors are linked through a stimulatory guanine nucleotide regulatory protein (G_s), and α_2-adrenergic receptors are linked through an inhibitory guanine nucleotide regulatory protein (G_i) to adenylyl cyclase. Thus, catecholamine occupancy of these receptors leads to increments or decrements in adenosine 3′,5′-cyclic phosphate (cyclic AMP) and in the corresponding cyclic AMP-dependent protein kinase activities. In contrast, α_1-adrenergic receptors are linked to phospholipase C activity, and the second messengers are thought to include inositol trisphosphate (which mobilizes intracellular calcium) and diacylglycerol (which activates protein kinase C).

A detailed discussion of the adrenergic receptor mediation of all of the actions of the catecholamines is beyond the scope of this review, but some examples will be mentioned. Norepinephrine and epinephrine are mixed agonists; they interact with both α- and β-adrenergic receptors. In general, epinephrine has a higher affinity for receptors and is more potent. Catecholamines increase the rate and force of myocardial contraction (β_1) and produce vasoconstriction (α) in most vascular beds, although vasodilation (β_2) occurs in some vascular beds, such as those of skeletal muscle. Norepinephrine produces increased vascular resistance and blood pressure (systolic and diastolic); the increased blood pressure reflexively limits the increase in heart rate. Probably because it has a substantially higher affinity than norepinephrine for β_2-adrenergic receptors, epinephrine produces a different hemodynamic pattern: increased heart rate and cardiac output with increased systolic but decreased diastolic blood pressure.

Catecholamines increase plasma glucose concentrations through complex actions.[14,15] These involve both the stimulation of hepatic glucose production (both glycogenolysis and gluconeogenesis are stimulated) and the limitation of glucose use and include both direct and indirect (other hormone-mediated) actions. The direct actions are largely mediated through β_2-adrenergic mechanisms. Foremost among the indirect actions is α_2-adrenergic limitation of insulin secretion. This permits the glycemic response to occur, but some increase in insulin secretion normally limits the magnitude of the glycemic response. Generally through β-adrenergic mechanisms, catecholamines also stimulate lipolysis, keto-

genesis, and thermogenesis and mobilize gluconeogenic precursors including lactate, alanine, and glycerol.

Pheochromocytoma

Pheochromocytomas are catecholamine-releasing tumors of chromaffin cells that typically produce hypertension.[5-8] They are an uncommon cause of hypertension; perhaps 1 in 1,000 hypertensive patients has a pheochromocytoma. Yet, it is important to detect a pheochromocytoma for several reasons. First, hypertension due to a pheochromocytoma is usually curable by the surgical removal of the tumor. Second, persons with a pheochromocytoma are at ongoing risk for a lethal hypertensive paroxysm. Third, some pheochromocytomas (perhaps 5% to 10%) are malignant; early detection and removal would be expected to reduce the frequency of metastatic disease. Parenthetically, malignancy is established convincingly only by proven metastases; histologic criteria in the primary tumor are not reliable. Fourth, the presence of a pheochromocytoma can be a clue to the presence of associated endocrine or nonendocrine familial disorders.

Pheochromocytomas are components of the multiple endocrine neoplasia (MEN) type II and type III syndromes.[16] These are inherited as autosomal dominant traits. Type II MEN includes medullary carcinoma of the thyroid, primary hyperparathyroidism, and pheochromocytoma. Type III MEN (sometimes called MEN IIB) includes medullary carcinoma of the thyroid, multiple mucosal neuromas, and pheochromocytoma. Obviously it is fundamentally important to exclude pheochromocytoma before a neck operation in a member of such a family because an unrecognized pheochromocytoma could result in a fatal hypertensive paroxysm during the operation. Pheochromocytomas are not a component of the MEN I syndrome (functioning pituitary and pancreatic islet adenomas and hyperparathyroidism). Familial pheochromocytomas also occur as an isolated disorder, with varying frequency in kindreds with the von Hippel-Lindau syndrome, and uncommonly in patients with neurofibromatosis.

The gene for MEN II has been mapped to a region on chromosome 10. With this knowledge, restriction fragment-length polymorphism analysis has been used to identify patients at risk. Although the genetic basis of chromaffin cell tumor formation is not known, a mechanism involving the inactivation of tumor suppressor genes has been proposed. Indeed, in pheochromocytomas, a loss of heterozygosity has been found on several chromosomes (1p, 3p, 17p, and 22q).[16]

Pathology

Pheochromocytomas arise from chromaffin cells. Chromaffin cells are widespread and associated with sympathetic ganglia during fetal life. Most chromaffin cells degenerate postnatally; the major remaining clusters of chromaffin cells make up the adrenal medullae, although some extra-adrenal chromaffin cells persist throughout life.[1,17(pp77-78)] Thus, it is not surprising that 90% of pheochromocytomas arise in the adrenal medullae. Extra-adrenal pheochromocytomas (paragangliomas) have been found in sites ranging from the carotid body to the pelvic floor. Most, however, are associated with sympathetic ganglia, including the organ of Zuckerkandl near the aortic bifurcation, in the abdomen, and most of the others with ganglia in the posterior mediastinum.

Multiple pheochromocytomas occur in fewer than 10% of cases. Multiple tumors, however, particularly bilateral adrenomedullary tumors, are the rule in familial pheochromocytoma.[18] Indeed, bilateral adrenomedullary hyperplasia, thought to be a precursor to pheochromocytoma, has been found in members of affected families.[19]

The vast majority of pheochromocytomas release norepinephrine, and most also release epinephrine. Rarely, a pheochromocytoma releases epinephrine predominantly or even exclusively.[20] This is uncommon and cannot be identified clinically with confidence. A clinically typical epinephrine-producing pheochromocytoma (described later) can produce substantial amounts of norepinephrine as well.[21]

The clinical manifestations of pheochromocytomas are commonly due to the effects of released catecholamines (or perhaps other substances) and only rarely to mass effects of the tumor. Some pheochromocytomas are discovered at autopsy or incidentally at a surgical procedure. Whether these tumors synthesized catecholamines that were degraded within the tumor and not released, released catecholamines at rates that did not produce plasma levels sufficient to cause clinically apparent effects, or caused clinical manifestations that the physician failed to recognize is conjectural. Retrospective analysis of such cases has often disclosed clues to the presence of a pheochromocytoma.[22] Clearly, physicians must have a high index of suspicion if this often curable disease is to be diagnosed appropriately.

Clinical Manifestations

The symptoms of pheochromocytomas are typically paroxysmal. Most patients feel well most of the time but have symptomatic episodes that usually last only a few minutes, although they can persist for an hour or longer. The common paroxysmal symptoms are headache, palpitations, and diaphoresis. The vast majority of affected patients have at least one of these symptoms, most have two, and many have all three.[5] Other symptoms include anxiety, abdominal or chest pain, visual changes, constipation or diarrhea, weakness, and dyspnea. Electrocardiographic changes suggestive of myocardial infarction have been described, and cardiac failure occurs. Cardiac failure has been attributed to a specific, reversible cardiomyopathy in some patients.

Symptomatic paroxysms are typically associated with increments in blood pressure, often with little if any tachycardia. Hypertension is sometimes truly intermittent. In many cases, hypertension is sustained but the blood pressure shows pronounced fluctuations with peak values occurring during symptomatic episodes. In a given patient, plasma catecholamine levels are higher during symptomatic, hypertensive episodes than during asymptomatic, less hypertensive, or even normotensive intervals. The event(s) that precipitates episodic catecholamine release is usually not identifiable. The apparent association with stress is difficult to understand because the tumors are not thought to be innervated.

The metabolic features of pheochromocytoma include an increased metabolic rate—some patients have heat intolerance, weight loss, or both—and insulin resistance. Glucose intolerance and fasting hyperglycemia are not uncommon, but symptomatic diabetes is unusual and probably reflects a coexistent defect in insulin secretion, that is, coexistent diabetes mellitus.

Predominantly epinephrine-releasing pheochromocytomas can produce different paroxysms.[20,21] These may include hypotension, prominent tachycardia, noncardiac

pulmonary edema, and cardiac arrhythmias. It is conceivable that tumor products in addition to epinephrine might contribute to these manifestations.

Diagnosis

The diagnosis of pheochromocytoma (Table 1) is based on clinical suspicion and biochemical confirmation. In general, imaging studies should be used only to provide anatomic localization of pheochromocytomas known to be present, or at least strongly suspected, on the basis of clinical and biochemical evidence.

TABLE 1.—*Diagnosis of Pheochromocytoma*

Clinical Suspicion
- Paroxysmal symptoms—especially with hypertension
- Hypertension that is intermittent, unusually labile, or resistant to therapy
- Family history of pheochromocytoma or associated conditions
- Incidental adrenal mass (rarely a pheochromocytoma in the absence of any of the above)

Biochemical Confirmation
- Plasma norepinephrine and epinephrine levels (± dopamine)
  - Specimen taken with patient in the basal state (and supine position) and, if possible, during a paroxysm
  - Radioenzymatic or HPLC method
  - Note blood pressure, heart rate, and any symptoms
- Urine norepinephrine and epinephrine levels (± dopamine)
  - Can be used as the initial test
  - Particularly indicated if plasma values are normal or equivocal, but repeated plasma measurements are an alternative

Anatomic Localization
- Computed tomography or magnetic resonance imaging
  - Of the abdomen, including the adrenal glands, initially; of the pelvis and thorax if the abdomen is normal
  - Indicated in the absence of biochemical evidence only if clinical suspicion is high (positive family history)
- [^{131}I]*m*-Iodobenzylguanidine scintigraphy

HPLC = high-pressure liquid chromatography

A clinical suspicion of pheochromocytoma is usually based on paroxysmal symptoms, especially if these are associated with hypertension. The disease is also suspected in a patient with hypertension that is intermittent, unusually labile, or resistant to therapy or in a patient with a family history of pheochromocytoma or a family or personal history of disorders known to be associated with pheochromocytoma—MEN II, MEN III, neurofibromatosis, von Hippel-Lindau syndrome. Adrenal masses are not infrequently found with modern imaging procedures done for other reasons.[23] These lesions are rarely pheochromocytomas in the absence of other clinical clues to that diagnosis, but it must be considered.[23]

The measurement of catecholamines or catecholamine metabolites (metanephrines or VMA) in 24-hour urine specimens is the traditional approach to a biochemical confirmation of suspected pheochromocytoma. The frequency of falsely normal findings is somewhat higher with VMA determinations. Nonetheless, the excretion of all three is substantially increased in most patients with pheochromocytomas.[7,24] Most laboratories now use high-pressure liquid chromatography (HPLC) methods employing electrochemical detection to measure catecholamine concentrations in urine. These provide individual measurements of norepinephrine, epinephrine, and dopamine levels and are the preferred analytic approach.

With the development of sufficiently sensitive methods, including single isotope derivative (radioenzymatic) and HPLC assays, plasma catecholamine measurements were effectively introduced into the biochemical diagnosis of pheochromocytoma.[2,5,6] Although radioenzymatic methods are more sensitive, most HPLC methods are sensitive enough to answer the clinical question: are the catecholamine levels elevated? Furthermore, they are less expensive and time consuming and easier to maintain. As with measurements in urine, these provide individual values for the plasma concentrations of norepinephrine, epinephrine, and dopamine.

The choice between plasma and urinary catecholamine measurements is largely subjective. Plasma catecholamine values were judged superior to urinary VMA and total metanephrine values in one comparative study.[5] In another study, 24-hour urinary norepinephrine values were judged slightly superior to plasma norepinephrine values.[25] Plasma measurements are more convenient, although certain precautions, discussed shortly, are necessary. In theory, because they provide an index of catecholamine release integrated over time, urinary measurements might reflect intermittent plasma catecholamine elevations that could be missed by plasma measurements, which provide information relevant only to a time frame of a few minutes. On the other hand, because only a small fraction of circulating catecholamines is excreted in the urine, it could be reasoned that 24-hour urine measurements might miss substantial but short-lived plasma catecholamine elevations. Thus, it is conceivable that plasma and urinary measurements might provide complementary information.

Most patients with a pheochromocytoma have notably elevated plasma catecholamine values (Figure 2). Three points warrant emphasis, however. First, some patients with pheochromocytomas and typical histories of paroxysms have normal plasma catecholamine concentrations during an asymptomatic, normotensive interval. When tested during a hypertensive paroxysm, such patients have elevated values.[6] Second, some patients, typically those investigated because of a family history of pheochromocytoma and known to have another component of a given syndrome such as MEN, have no symptoms or signs and have normal plasma (and urine) catecholamine levels but are found to have a pheochromocytoma. These are not innocent tumors; lethal hypertensive paroxysms have occurred in such previously asymptomatic patients. Third, as mentioned earlier, patients thought to have predominantly epinephrine-secreting pheochromocytomas on clinical grounds can also have substantial overproduction of norepinephrine.[21]

Most provocative and suppressive tests for pheochromocytoma[2,6] are only of historical interest. The clonidine suppression test[5] is used by some physicians, however. This test is based on the premise that the α_2-adrenergic agonist clonidine suppresses sympathetic outflow from the central nervous system and, thus, suppresses plasma catecholamine levels in persons who do not have pheochromocytomas but does not suppress elevated levels derived from pheochromocytomas, which are not thought to be innervated. The clonidine suppression test, however, provides only marginally better sensitivity and specificity than plasma catecholamine measurements alone,[5] and false-positive and false-negative results sometimes occur.[26] Indeed, it is conceivable that multiple plasma catecholamine measurements alone might yield

information comparable to that derived from the test. Furthermore, the drug commonly produces sedation and can produce hypotension (especially in patients treated with diuretics) or bradycardia (especially in patients treated with a β-adrenergic antagonist). Although the results of the clonidine suppression test in a large group of patients with proven pheochromocytomas[5] are rather impressive, the test has not been assessed critically in the patients in whom it is most needed—those with a compatible clinical picture but equivocal plasma catecholamine levels.

My clinical experience with plasma catecholamine measurements in the diagnosis of pheochromocytoma, summarized in Figure 2, might appear to conflict with the large experience of Bravo and colleagues, who found less overlap in values between those persons with and without pheochromocytomas.[5] This probably reflects differences in referral patterns, however. I am an endocrinologist and do not have a research program in hypertension or pheochromocytoma. Therefore, I am most often asked to see patients with endocrinologic disorders, including MEN syndromes, and other syndromes associated with pheochromocytoma, such as the von Hippel-Lindau syndrome and neurofibromatosis, as well as patients in whom pheochromocytoma has been suspected but not confirmed. On the other hand, I do not routinely see all patients referred to our medical center (Washington University) for surgical treatment of pheochromocytoma. Thus, the experience reflected in Figure 2 probably includes a disproportionate number of patients in whom the diagnosis of pheochromocytoma represented a diagnostic challenge. Nonetheless, this does not negate the fact that occasional patients with typical histories of pheochromocytoma have normal plasma catecholamine levels when they are normotensive and asymptomatic.

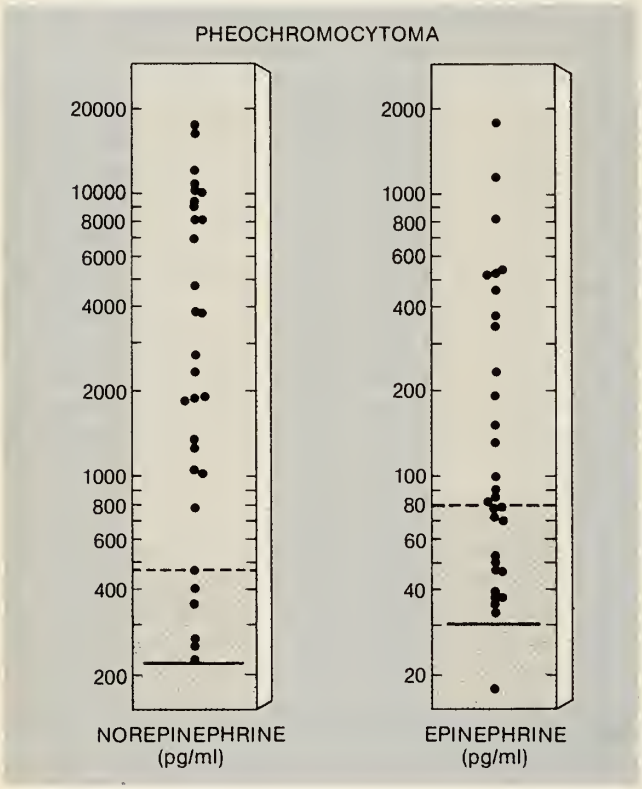

Figure 2.—Plasma norepinephrine and epinephrine concentrations (radioenzymatic method) in 30 patients with pheochromocytomas are shown. Note the semilogarithmic scales. The interrupted horizontal lines are 3 standard deviations above the means (solid horizontal lines) of data from 165 normal humans whose specimens were obtained with them in a supine position.

Strict attention to the details of specimen collection, handling, and storage, the sources of possible biologic variation, and the effects of drugs is critical if diagnostic error is to be avoided in the biochemical assessment of patients with suspected pheochromocytomas. This applies to both plasma and urinary catecholamine measurements but is perhaps more critical with the former.

Possible errors in the use of plasma catecholamine measurements in the diagnosis of pheochromocytoma are outlined in Table 2. From a technical standpoint, it is critical that the patient be in the supine position before and during specimen taking. Plasma norepinephrine and epinephrine concentrations *double* when a normal person stands.[2] Catecholamines are readily oxidized. They are most stable at low temperature and low pH and in the presence of an antioxidant. Furthermore, erythrocytes contain catechol-*O*-methyltransferase. In whole blood, catecholamines deteriorate at a rate of about 30% per hour at room temperature.[27] Therefore, blood specimens for plasma catecholamine determinations should be drawn into iced tubes containing an anticoagulant and an antioxidant and the plasma separated, preferably in a refrigerated centrifuge, promptly. Once separated, plasma should be frozen quickly. Catecholamines deteriorate at a rate of about 5% per month at −20°C. At −70°C they are stable for at least a year.[27] Finally, as mentioned earlier, only radioenzymatic or HPLC methods are suitable for measuring catecholamine concentrations in plasma at this time.

TABLE 2.—*Possible Errors in the Use of Plasma Catecholamine Measurements in the Diagnosis of Pheochromocytoma*

Technical
Obtaining specimen—patient must be in supine position (at least 20 minutes); an IV line preferred
Specimen handling—iced, special tubes required; prompt transport of specimen and separation of plasma necessary
Specimen storage— −20°C (hours to days); −70°C (longer)
Analytic method—HPLC or radioenzymatic method necessary
Biologic Variation—normally marked; increased levels with
Acute physical or mental stress
Chronic disorders
Drug-induced Variation
Catecholamines and related compounds
Methyldopa, isoproterenol, terbutaline, metaproterenol
Increased catecholamine release
Sympathomimetics—ephedrine, amphetamines, tyramine
Vasodilators—nitrates/nitrites, hydralazine, minoxidol, methylxanthines, phenothiazines, calcium channel antagonists
α-Adrenergic antagonists—phentolamine, phenoxybenzamine, prazosin
Diuretics (if produce sodium depletion)
Cigarette and marijuana smoking, caffeine ingestion
Decreased catecholamine clearance
β-Adrenergic antagonists—propranolol
Tricyclic antidepressants, reserpine, guanethidine, cocaine

HPLC = high-pressure liquid chromatography, IV = intravenous

The biologic variation in plasma catecholamine concentrations can be pronounced. For example, plasma epinephrine concentrations increase as much as 100-fold during hypoglycemia.[2] Smaller, but still substantial, increments in norepinephrine and epinephrine levels occur rapidly during

common activities.[2] Elevated plasma catecholamine levels have been well documented during acute mental and physical stress. Stable elevations also occur in several chronic diseases such as hypothyroidism, congestive cardiac failure, chronic obstructive pulmonary disease, anemia, and duodenal ulcer.[2]

If at all possible, specimens should be obtained when patients are drug-free. Most antihypertensive drugs (other than clonidine) and many other drugs can elevate plasma (and urinary) catecholamine levels. Some of the mechanisms are summarized in Table 2. Although the magnitude of the plasma catecholamine elevations varies among the drugs, all can produce a false-positive test. If the physician is compelled to treat hypertension before measuring catecholamines, clonidine is the drug of choice because it will not produce a false-positive result.

It is my practice to obtain specimens for determining plasma norepinephrine and epinephrine levels in the basal state when pheochromocytoma is suspected. Substantial elevations over reference values provide strong support for the diagnosis of pheochromocytoma and are commonly found in affected patients. Specimens are also obtained during a symptomatic paroxysm, if possible. Interpreting such values, however, is more judgmental because reference values cannot be defined precisely. Thus, the biochemical diagnosis of pheochromocytoma is most convincingly confirmed if plasma catecholamine levels are elevated in the basal state and rise further during symptomatic episodes.

It is useful to record the blood pressure and note whether or not symptoms are present when plasma specimens for catecholamine measurements are drawn from a patient suspected of having a pheochromocytoma. Normal plasma (or urinary) catecholamine values obtained when the patient is normotensive and free of symptoms do not exclude the presence of a pheochromocytoma. Because 24-hour urinary catecholamine measurements might detect intermittent catecholamine release missed by plasma sampling, these should be done if plasma catecholamine levels are normal but clinical suspicion is high. Alternatively, serial plasma specimens could be taken.

Substantial plasma norepinephrine elevations are required to produce hypertension in normal persons.[2] (Epinephrine elevations do not produce diastolic hypertension.) It is reasonable, therefore, to consider normal or even moderately elevated plasma norepinephrine levels measured when the patient is hypertensive to be evidence that the hypertension is not the result of a pheochromocytoma.

Most patients ultimately proved to have pheochromocytomas have distinctly elevated plasma and urinary catecholamine levels. The considerations raised in the preceding paragraphs apply to patients in whom the diagnosis is less clear and to the always difficult problem of the degree of certainty of a negative conclusion. Obviously, one can never be absolutely certain during life that a given patient does not have a pheochromocytoma. As in many other areas of medicine, clinical judgment must be based on probability.

Plasma chromogranin A concentrations are also elevated in patients with pheochromocytomas.[28] In an initial experience,[28] the diagnostic sensitivity and specificity of chromogranin A levels were found to be high.

Finally, with respect to the diagnosis, the screening of all hypertensive patients for pheochromocytoma is not indicated. The prevalence of pheochromocytoma is so low in the hypertensive population that the vast majority of positive screening tests would be false-positive.[2,6] The inconvenience, discomfort, and expense of further testing, as well as the risk of therapeutic misadventure, outweigh the benefit of detecting a rare pheochromocytoma in a patient with no clinical clues to that diagnosis. Rather, physicians should increase the prevalence of pheochromocytoma in the population tested on the basis of clinical suspicion as discussed earlier (see also Table 1).

Anatomic Localization

Given the biochemical confirmation of pheochromocytoma, anatomic localization of the tumor is the next step. Computed tomography (CT) is the most commonly used imaging technique and localizes the vast majority of pheochromocytomas. For practical purposes, it localizes all adrenomedullary pheochromocytomas, but it is less effective for extra-adrenal tumors. Magnetic resonance imaging (MRI) may well become the preferred primary imaging technique because it appears to identify adrenomedullary lesions at least as well as CT does and may identify extra-adrenal tumors more effectively.[29,30] Furthermore, magnetic resonance often produces distinctive images—hyperintense T2-weighted images—of pheochromocytomas, as shown in Figure 3.[30] Scintigraphy using *m*-iodobenzylguanidine (MIBG) labeled with iodine 131 has the conceptual advantage of measuring function rather than anatomy and permits scanning of the entire trunk. It appears to be superior to CT, and perhaps MRI, in localizing a recurrent or metastatic pheochromocytoma[30] and at least superior to CT in

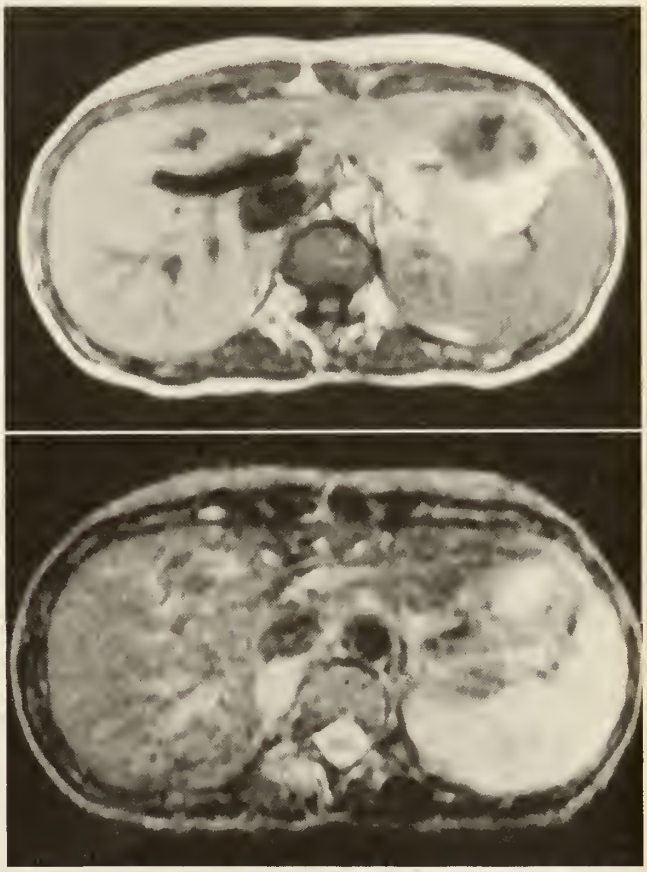

Figure 3.—Magnetic resonance images are shown in a patient with a right adrenomedullary pheochromocytoma. The tumor is visible on the T1-weighted image **(top)** but is much more prominent on the T2-weighted image **(bottom)**.

localizing other extra-adrenal tumors. In general, CT and [^{131}I]MIBG scans are complementary.[30-32] The availability of [^{131}I]MIBG is limited, however, the test is expensive, and it requires several days. Iodine must be given to the patient to protect the thyroid gland from the radioactive iodine. Thus, [^{131}I]MIBG scanning will probably be reserved for difficult cases for the foreseeable future.

The concept that imaging procedures should be reserved for patients with clinical and biochemical evidence indicating the presence of a pheochromocytoma has been emphasized throughout this review. Benign, nonfunctional adrenal masses are not uncommon (at least 2% of abdominal CT scans).[23] Thus, if imaging is done before the results of biochemical testing are known, adrenal lesions will be identified in some patients subsequently found to have no biochemical support for a diagnosis of pheochromocytoma. This will require, at a minimum, additional testing to exclude the overproduction of adrenocortical hormones and serial follow-up imaging. It could lead to an unnecessary operation. Thus, the rule is biochemical confirmation of pheochromocytoma first, imaging second. The exception to the rule is a member of a family with a syndrome that includes pheochromocytoma, particularly if that family member is known to carry the abnormal gene—such as a member of a MEN II family who has medullary carcinoma of the thyroid. An imaging procedure should be done in such a person even in the absence of paroxysmal symptoms, hypertension, or catecholamine elevations because the probability that any adrenal mass identified is in fact a pheochromocytoma is high.

Treatment

Treatment is the surgical removal of the pheochromocytoma. Many physicians believe that preoperative α-adrenergic blockade reduces surgical morbidity and mortality, although critical evidence to support this belief is lacking.[33] The premises are that preoperative α-adrenergic blockade will permit a re-expansion of intravascular volume, for which there is evidence,[23] and reduce the frequency and severity of intraoperative hypertension. The long-acting, orally effective α-adrenergic antagonist phenoxybenzamine hydrochloride (Dibenzyline) is most often used. Starting with 10 mg twice a day, the dose is increased until the blood pressure is controlled and symptomatic paroxysms are prevented. A failure of hypertension to respond to phenoxybenzamine administration should prompt a reassessment of the diagnosis of pheochromocytoma or of the assumption that the hypertension is due only to a pheochromocytoma known to be present.[34] Side effects include postural hypotension and, sometimes, the emergence of cardiac arrhythmias. A β-adrenergic antagonist such as propranolol hydrochloride can be added if tachycardia or arrhythmias become a problem.

Some have advocated the use of the α_1-adrenergic antagonist prazosin hydrochloride (Minipress) or the tyrosine hydroxylase inhibitor α-methyl-L-tyrosine (metyrosine; Demser), rather than phenoxybenzamine, to prepare patients for surgical excision. This use of either drug has been criticized because of the occurrence of pressor episodes during the operation.[35,36] These, however, can occur in patients treated with phenoxybenzamine.

Pheochromocytoma operations are high-risk procedures that require a surgeon and an anesthesiologist who have experience with the disorder. Careful monitoring of the blood pressure and cardiac rhythm is fundamental. Plasma catecholamine levels vary widely[37]; severe hypertension, arrhythmias, or both can occur during the induction of anesthesia, during manipulation of the tumor, or without obvious explanation. Hypertensive episodes can be treated with the rapid-acting α-adrenergic antagonist phentolamine (Regitine) mesylate or another agent given intravenously. Arrhythmias can be treated with a β-adrenergic antagonist or another antiarrhythmic drug. Given experience and vigilance, the operative mortality rate is low, about 1%.[4]

Whether due to postoperative stress, an expanded catecholamine pool, or both, plasma and urinary catecholamine values often remain elevated for about a week after the operation. Therefore, clinical and biochemical reassessment should be delayed for several weeks. Reported cure rates vary from about 67% to 85% of patients. About 5% to 10% of patients thought to be cured suffer recurrence.[8] Thus, lifelong follow-up is indicated. Persistent hypertension can be the result of a missed pheochromocytoma, a surgical complication resulting in renal ischemia,[34] or underlying essential hypertension.

The biochemical effects of unresectable pheochromocytomas can be treated with adrenergic antagonists. Malignant pheochromocytomas are generally resistant to radiotherapy and to chemotherapy, although responses to combination chemotherapy with cyclophosphamide, vincristine sulfate, and dacarbazine have been reported.[38] The course of patients with metastatic pheochromocytomas is variable. Some patients die within months; others live for more than a decade. The five-year survival rate averages about 45%.[8]

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A MESSAGE

I watch the medication drip
from eight I.V.'s
plugged into your body.
If you die now, would all this
medicine harden inside you?
There's a moth in your wrist
pattering its wings against
the gauze of your skin.
In seventh grade biology class
my teacher described the sound
a human heart makes as "lub-dub."
The blood goes in and out
of the chambers, lub-dub, lub-dub.

When death comes does it
cauterize an opening in the air
so the spirit can ascend
from this wounded world cleanly
like the incision that trusses your heart
in the cage of your chest?
I take your hand.
You beat a message.
It could mean stay.
It could mean go.

M. WYREBEK©
Sterling, Massachusetts

Epitomes

Important Advances in Clinical Medicine

Occupational Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in occupational medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in occupational medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Occupational Medicine of the California Medical Association, and the summaries were prepared under its direction.

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California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

The New Workplace Accommodation Guidelines

In the past, there have been many reasons for physicians to recommend that a job applicant not be hired. These have included a current inability to meet the physical exertion requirements, preexisting disease that may worsen, potential adverse effects of the job on a patient's disease (for example, a person with asthma may be bothered by sulfur dioxide), enhanced risk of developing an occupational injury, danger to the public, and so forth. These concerns have fostered two adverse side effects—job discrimination and paternalism. Job discrimination against persons with physical impairments was not always rationally based, and certain groups, even in the absence of disease, were precluded from some jobs. For example, because women are only about 60% as strong as men, all women (even strong women) were considered unsuitable for certain manual lifting jobs. Furthermore, since only women become pregnant, certain actions were taken to protect fetuses from toxins by excluding fertile women. Paternalistic attitudes abounded towards "the handicapped," making them worthy of "charity" and special protection. Physicians often used different medical standards in considering job fitness, depending on the setting.

Following several decades of concern, two recent events have changed the outlook. The United States Supreme Court, in the *Johnson Controls* case, ruled against a policy of excluding potentially pregnant women from jobs with poorly controllable exposure to lead, a transplacental fetal toxin. Controlling the risk to the fetus did not warrant potential limitation of job opportunities, the court stated. The federal Americans with Disabilities Act (ADA) was signed and implementation guidelines were issued. In addition to establishing specific regulations, passage of ADA mandates a change in philosophy. Employers and physicians must now think very clearly about the process of medical evaluation for a job.

Medical evaluations under the ADA cannot be done until there has been a preliminary job offer. The employer technically should be "blind" to medical information while deciding who should be offered a job. This eliminates the traditional cursory "pre-employment examination." The job offer may be made contingent on passing a job-relevant examination, however. This requires that the examining physician thoroughly understand the specific job, its exposures, and its physical demands, which often may mandate a visit to the job site. The physician who classifies a person as medically unfit for a job must now be prepared to justify this recommendation by stating that the worker cannot now meet the job's physical requirements or that there is substantial risk of future harm in the job. The latter is based on four criteria: what is the duration of the risk; how severe is the potential harm; how likely is it to occur; and how soon might it occur? These considerations may be complex.

Employers cannot simply decline to hire persons who do not meet stated requirements or who are perceived to be at increased risk. Instead, they are obligated to make "reasonable accommodation" to alter the job to enable the worker to accept it. Employers also must make adjustments in job application procedures to assure equal access to the disabled. Physicians can enhance the hiring of persons with disabilities by providing clear statements of their abilities rather than focusing on specific diagnoses or impairments. For example, if a person could not safely lift 45 kg (100 lb), the examining physician should state how much could be lifted safely. Physicians can offer advice on the degree of irritant chemical exposure control that would let a person with asthma or psoriasis work. Careful medical examination and reporting can help ensure that employers do not discriminate.

Although there will still be situations in which physicians must recommend against placement, they now must think carefully about this decision. Physicians also must be prepared to counsel patients accurately about risks, so that these potential workers can make informed decisions about the amount of risk that is personally acceptable to them.

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Needle-stick Injuries Among Health Care Professionals

NEEDLE-STICK ACCIDENTS account for a substantial number of injuries among hospital workers each year. Investigators have found that nursing personnel report nearly 30 needle sticks per 100 full-time-equivalent employees per year. Potential exposures are not limited to needle sticks alone, because manipulation of other sharp instruments or mucous membrane exposures to infected bodily fluids also can result in the transmission of infectious diseases. Quantifying the precise risk for disease transmission following mucocutaneous exposures is difficult because many go unreported. House staff, for example, fail to report between 60% and 95% of exposures.

Although underreporting has complicated the analysis of risk for transmission of disease, risk factors for injury have been described. Needle-stick injury often occurs during unnecessary handling of a used needle. Needles should, therefore, never be recapped or otherwise unnecessarily handled after use. Care should be taken to place used needles in puncture-resistant containers as soon as possible following a procedure. Persons doing procedures involving needles or other sharp instruments should be responsible for proper disposal. Multiple-step processes, such as obtaining central venous access, should be done with forethought and care so the risk for accidental percutaneous exposure is limited. Routine drawing of blood also should be planned carefully. For example, recent studies document that it is not necessary to change needles to avoid contamination when inoculating blood cultures. Hospital personnel should be given specific instruction in methods and techniques to avoid potential exposures. This important health education process should be incorporated into the orientation process for new employees, as well as into periodic departmental meetings as mandated by recent Occupational Safety and Health Administration (OSHA) requirements.

While there is considerable evidence to suggest that hepatitis B is readily transmissible by needle-stick or other mucocutaneous exposure, the potential for transmitting the human immunodeficiency virus (HIV) is not as well known. For example, the potential for transmitting hepatitis B from an infected patient to a health care professional through needle stick has been variously estimated at between 5% and 35%. By comparison, the risk of transmitting HIV by a needle stick approached 0.3% in one large prospective study. Because there are an estimated 800,000 needle-stick injuries per year and an estimated prevalence of HIV infection approaching 2% among hospital patients, one author has estimated a potential for 48 cases of HIV seroconversion per year among health care workers in the United States.

Although there is considerable interest in developing new technologies to prevent all mucocutaneous exposures, the first line of defense for health care workers is prevention. High-risk areas, such as operating rooms, emergency departments, and intensive care units, should be designed so that there is adequate lighting and that puncture-proof sharps disposal containers are easily accessible. Personnel should be advised of the importance of complying with the universal precautions guidelines promulgated by the Centers for Disease Control, and efforts should be made to increase the use of the new "needleless" systems that minimize exposure to used needles.

The benefit of prophylaxis following percutaneous exposure to hepatitis B infection is well documented. Nonvaccinated employees should be offered hepatitis B immune globulin and the hepatitis B vaccination series. A highly effective vaccine exists for this disease, however, and all personnel at risk should be offered it before starting work. Because there are no specific antibody preparations for prophylaxis following HIV exposure, the benefit of using zidovudine (AZT) for postexposure prophylaxis for health care professionals with occupational exposure to HIV is now being evaluated in an open trial sponsored by the Centers for Disease Control. If any degree of efficacy can be shown, it is likely that the potential for long-term benefit will far outweigh any toxicity from short-term AZT therapy. While data are still incomplete regarding efficacy, many hospitals are offering AZT prophylaxis to employees who have sustained a significant needle-stick or mucous membrane exposure to HIV-infected materials.

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Ergonomics—Prevention of Work-Related Musculoskeletal Disorders

CHRONIC MUSCULOSKELETAL disorders associated with repetitive work are of increasing concern to industry, employees, workers' compensation insurance carriers, and regulatory agencies. The incidence of these conditions, known collectively as cumulative trauma disorders, has been increasing at a rate of about 20% per year for the past seven years and has surpassed all other reported occupational illnesses. The highest rates are found in manufacturing industries such as meat processing and industries with assembly-line work; in the past three years, reports also have been increasing in video display terminal-intensive tasks.

The best approach to cumulative trauma is prevention. Risk factors associated with cumulative trauma disorders, repetition of motion, extremes in joint position, prolonged constrained posture, mechanical pressure points, and vibration, can be decreased. These risk factors may also be influenced by job stress and work organization. Other methods of controlling these disorders include job rotation, job enlargement, and modifying the work-rest cycle.

If force is repeatedly applied over time to the same joint, muscle, tendon, or ligament, the cumulative force may cause soft-tissue microtears and trauma. The resulting injury and inflammatory response may lead to tendon and synovium

disorders, ligament sprains, muscle strains, bursitis, and nerve entrapments. Common sites of injury are the back, shoulder, elbow, and wrist. Treatments include rest of the affected limb through work restriction and judicious use of splints; physical therapy; nonsteroidal anti-inflammatory agents; ice; corticosteroid injections; and surgery. After the symptoms have resolved, physical therapy should be directed at muscle strengthening to prepare the person to return to work. If modified duty work is not available during treatment, the employee may not be able to work. If the disorder was not triggered by a specific event or an underlying medical condition, the physician should recommend that the work be permanently modified to prevent recurrence.

Although relatively simple interventions may be called for (such as wrist supports and work breaks), the most successful programs are well coordinated and involve medical surveillance, employee training, job analysis, engineering controls, and administrative controls. The best programs have small but empowered ergonomics teams that include employees, supervisors, engineers, and health and safety personnel. Part of the success of these programs is thought to be because employees aid in evaluating the tasks and implementing solutions.

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Resurgence of Work-Hardening Programs

WORK-HARDENING programs have undergone a resurgence in popularity because of their efficacy in rehabilitating injured people when a program is appropriately organized. The essential components of work-hardening programs are physical reconditioning, aerobic conditioning, work simulation, and education. Because it is directed at injured persons, work hardening must be goal-specific and job-directed. In addition to preparing the physical capacity for a person's return to work, activities should simulate realistic occupational situations. To accomplish this, the program must be intensive, operating five days per week, four to eight hours per day. The schedule is planned in a work-like manner; it may even be appropriate to have patients "punch in" and "punch out."

Functional capacity evaluations of strength, endurance, coordination, pace, and safety are included. The program should incorporate a customized obstacle course that includes lifting, carrying, twisting, crawling, bending, stooping, and other movements peculiar to a job. Normal performance levels are established by the therapist. The client is observed and timed moving through the course, and deviations from the norm are quantified so that they can be identified. Specialized equipment may be needed for certain simulations, but simple tools, such as bricks in a box, often suffice.

Work-hardening programs are designed to treat the entire spectrum of disability preventing a return to work. This contrasts with traditional rehabilitation programs, which focus on anatomic impairment. Standard physical therapy is less expensive, less intensive, and should be started soon after the injury. Work hardening is costly, with programs costing between $5,000 and $15,000, and is more appropriate when physical deconditioning and behavioral changes are preventing job return. This is typically about four months after an injury. When a patient is referred, the diagnosis must be firmly established and no further treatment, such as surgical procedures, is anticipated.

The programs usually last about three weeks. Dropout caused by lack of motivation occurs in 10% to 15% of participants. Encouragement and support from the referring physician and the insurance company are important. Specific goals should be set, and progress measured objectively. The patient must clearly understand that this is the most appropriate treatment and possibly the last chance for a return to gainful employment.

Credibility for work-hardening programs is established. About 80% of patients previously considered permanently disabled can be returned to employment. The fundamental philosophy responsible for this success is that measure of function, rather than discussion of pain, is the basis for treating an injured worker. All components of the program must be active, and the patient must be involved. The intensity and techniques are very different from the passive approach traditionally used to treat soft-tissue injuries. This is sports medicine for working people.

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Progress in Occupational Stress—Organizational Interventions

SEVERAL FACTORS are increasingly pushing occupational stress into the limelight. Workers' compensation claims for stress grew 700% between 1979 and 1989, driven by a greater awareness of its effects by both physicians and patients. Occupational health experts and others concerned with employee health and medical expenses are beginning to recognize that the hidden costs of stress are enormous. The contribution of stress to musculoskeletal disability as well as its role in organizational losses (productivity and lost work days) has catapulted this issue into the press. Most Fortune 500 companies now have developed some form of occupational stress program.

This attention intensifies the need to develop valid measures of stress and effective ways to control it. Traditional approaches to stress management have focused on modifying a person's response to reality through meditation, relaxation

techniques, exercise, or some other activity. Some short-term subjective benefits as well as temporary objective changes in blood pressure and electromyographic activity have been reported. Benefits at the organizational level, such as increased attendance, productivity, and reduced health care costs, have not been shown, however.

Recent investigations have explored ways to assess the sources of stress in the environment and to modify these. Research based on organizational interventions has yielded some encouraging results. New survey questionnaires, some of which are commercially available, can help determine the personal and organizational sources of stress; the data can be aggregated to provide an organizational stress profile that, in turn, can serve as the basis for planning interventions. One program resulted in reductions in all types of workers' compensation claims from 3.08 to 0.63 claims per month, with the average cost per claim dropping from $7,329 to $384. A key factor in the success of these programs is the commitment of managers to implement changes based on survey results.

Several recent studies have focused on job decision latitude (JDL) as a powerful predictor of workplace stress and future morbidity. Defined as an employee's ability to exercise decision-making authority at work and to choose the skills used on the job, JDL has been widely studied. In this model, work stress is the result of the interaction between JDL and job demands. Other factors being equal, a person with a highly demanding job but little control over its implementation is likely to be under more stress. Some of the other factors that are considered are lack of personal scheduling freedom and few opportunities for new learning on the job.

Low JDL has proved in several studies to be strongly associated with cardiovascular disease. A relationship between low JDL and cardiovascular disease in employed Swedish men was shown in one study. Another study reported a 22-year prospective study of pulp mill employees that showed higher mortality in people with low JDL. An interventional study showed that redesigning a work unit in order to increase JDL resulted in improved employee health as well as productivity.

Limited by their cost, complexity, and risk, organizational stress interventions are still relatively poorly studied and understood. They now represent the leading edge of occupational stress research and appear to hold promise for improved control of this problem.

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Mercury

MERCURY IS AN old occupational hazard that remains a problem in dental offices, health care institutions, and some homes.

Elemental mercury is a heavy metal that interferes with the sulfhydryl groups of proteins, particularly active sites of enzymes. The major manifestations of these chemical reactions are nephrotoxicity, primarily proteinuria and tubular necrosis, and neurotoxicity, which can be profound with high exposure. Cardinal symptoms of mercury toxicity include tremors, oral and gingival inflammation, ataxia, excessive and uncontrollable salivation, anorexia and weight loss, labile affect and irritability (erethism), pathologic shyness and avoidance of people, and acrodynia (erythema and painful desquamative dermatitis of the hands and feet). The deterioration of handwriting over time is often taken as one indication of subclinical effect. Persons with congenital mercury toxicity will have severe mental retardation and motor abnormalities, including disturbances in swallowing. Congenital organic mercury poisoning was perhaps most poignantly illustrated by the severe outbreak in Minamata, Japan, in the 1950s.

Organic mercury compounds are more rapidly absorbed than elemental mercury, especially by ingestion, and also are more toxic. These compounds are products of metabolism, accumulated in fish in mercury-contaminated rivers and estuaries, for example, and have been used as fungicides, particularly methylmercury on seeds. Organic mercury compounds are metabolized to mercury in the body, with the same toxicity as metallic mercury. Organomercurials were once used extensively as medications in the preantibiotic era and were responsible for many cases of toxicity. Organic mercury compounds are also used as preservatives in some latex paints and have also been associated with excessive exposure to mercury and clinical acrodynia.

Overt mercury toxicity has been reported in heavily contaminated dental offices, particularly where there has been an ineffective cleanup of spills. Most dental personnel are now aware of the hazard and often request blood mercury determinations as screening tests during physical examinations. There is also a debate over whether the minute amounts of mercury that vaporize from dental amalgams in patients may be toxic; the best evidence to date suggests that this is not the case. In health care institutions, mercury remains a part of many instruments. In the home, mercury exposure has been associated with spilling small quantities kept in the home for hobbies, as a by-product of efforts at home smelting, and as a constituent of interior latex paint.

Mercury vaporizes at room temperature. Inhalation can be substantial, especially if the mercury is heated at the source. A recent severe case of home exposure involved a quantity of mercury inadvertently spilled into a space heater that became a source of exposure for many months.

Mercury levels in blood or urine do not correlate with symptoms, probably because toxicity is intracellular and much circulating mercury is bound with protein. Cases of mercury poisoning, however, will show elevated levels. Relatively low levels of exposure, with urine or blood levels just outside the range of a reference population, have not been associated with demonstrable abnormalities; levels may vary by laboratory, with 24-hour yields from urine ranging from 0 to 50 nmol per liter. Hair analysis is not reliable for clinical diagnosis.

Treatment of serious mercury intoxication should be left to physicians with experience in clinical toxicology. Chela-

tion with dimercaprol, penicillamine, or their analogues is generally attempted but is less successful in mercury than in lead toxicity, presumably because the mercury is more chemically reactive and likely to be bound. The chelating agents also carry the risk of severe side effects.

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Alerts, Notices, and Case Reports

Bradytachyarrhythmia as the First Manifestation of Acute Rheumatic Carditis in an Adult

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THE INCIDENCE OF rheumatic fever, a common and widespread disease in the late 19th and early 20th centuries, has been declining rapidly and seemingly disappeared in many Western countries, including the United Kingdom and North America, over the last 20 years.[1-3] A striking resurgence of acute rheumatic fever has been seen, however, in the intermountain areas of the continental United States and in Hawaii in recent years.[4-7] This case report alerts the medical community to the possibility of a widespread return of rheumatic fever, which many young physicians may never have encountered.[8-10]

Changing clinical manifestations of rheumatic fever, particularly in adults, have been reported in the United States and in Asian-Pacific countries over the last two decades, as compared with the classic pattern described in the literature.[11-14] Whereas various forms of bradytachyarrhythmias are not uncommonly encountered in clinical practice, this condition has seldom been documented as a dominant manifestation of acute rheumatic carditis. I report a patient presenting with such manifestations.

Report of a Case

A 55-year-old Chinese man was admitted to the Prince of Wales Hospital in April 1986 because of syncope with clouding of consciousness preceded by a 2-week history of general malaise and pyrexia but no sore throat. He had no history of rheumatic fever. On admission, he had a low-grade fever but no cardiac murmur. An electrocardiogram (ECG) revealed sinus tachycardia and complete atrioventricular (AV) block, with idiojunctional bradycardia at a rate of 35 per minute and a long period (3.6 seconds) of ventricular asystole (Figure 1). He had no response to intravenous atropine and, accordingly, temporary cardiac pacing was done. He had intermittent and self-remitting episodes of atrial fibrillation and flutter lasting for a few hours over the next three days (Figure 1). On day 3, he developed migratory polyarthritis involving the wrists, elbows, ankles, and shoulder joints. Two days later, pericarditis appeared, along with precordial pain, pericardial rub, and concave ST-segment elevation on the ECG (Figure 2).

The patient's laboratory results included a leukocyte count of 12,000 × 10^6 per liter (12,000 per cu mm), an erythrocyte sedimentation rate of 115 mm per h, and an antistreptolysin '0' titer of 333 U per ml (normal 240 U per ml). The results of serologic screening for rheumatoid factor, antinuclear factor, and elevated antivirus titers were negative. A throat swab culture found no evidence of streptococci. An echocardiogram confirmed the presence of pericardial effusion but had unremarkable intracardiac findings.

The patient's arthritis and pericarditis responded rapidly to rest and acetylsalicylate treatment (Table 1), which was started at 5.2 gm daily in divided doses and was tailed down over a period of 10 weeks. There was no clinical, radiologic, or echocardiographic evidence of cardiac decompensation. He remained in unstable supraventricular rhythm over the first 4 weeks, but stable sinus rhythm was restored by day 60. His erythrocyte sedimentation rate was normal at 6 months' follow-up. He has been followed regularly for 5 years and takes oral sulphonamide prophylactically because he is allergic to penicillin. He has had no relapse of cardiac arrhythmia or syncope, and there is no evidence of a residual valvular lesion on clinical examination or echocardiography.

Discussion

This patient had definite acute rheumatic fever diagnosed according to the revised Jones' criteria,[15] with polyarthritis, pericarditis, pyrexia, leukocytosis, a high erythrocyte sedimentation rate, and an elevated antistreptolysin '0' titer but no cardiac murmur (Table 2). Results of screening were negative for collagen vascular disease and viral infection. Tachyarrhythmias and conduction disorders, which closely followed the clinical course, appeared to be a consequence of the acute carditis. His subsequent progress with no recurrence of atrial fibrillation, flutter, or heart block on long-term follow-up supports this premise. This combination of arrhythmias in acute rheumatic fever has not been described previously.

Delayed AV conduction in the form of prolongation of the PR interval is a common feature of acute rheumatic fever. It is a minor diagnostic criterion and occurs with similar frequency in the polyarthritis of acute rheumatic fever with or without evidence of carditis.[16] High-grade AV block—especially of second degree (Wenckebach)—and, rarely, complete AV block in acute rheumatic carditis are well recognized. Their occurrence is less common, however, and usually of brief duration with no hemodynamic significance.[16]

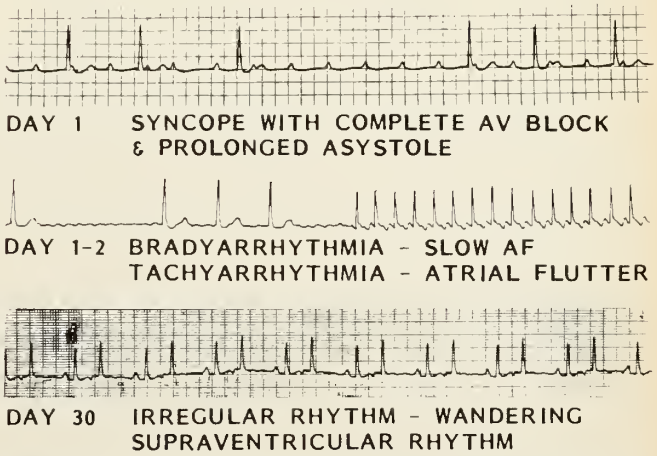

Figure 1.—Electrocardiographic rhythm strips show the bradytachyarrhythmias (day 1) and unstable supraventricular rhythm (day 30). AF = atrial fibrillation

(Woo KS: Bradytachyarrhythmia as the first manifestation of acute rheumatic carditis in an adult. West J Med 1992 Apr; 156:413-415)

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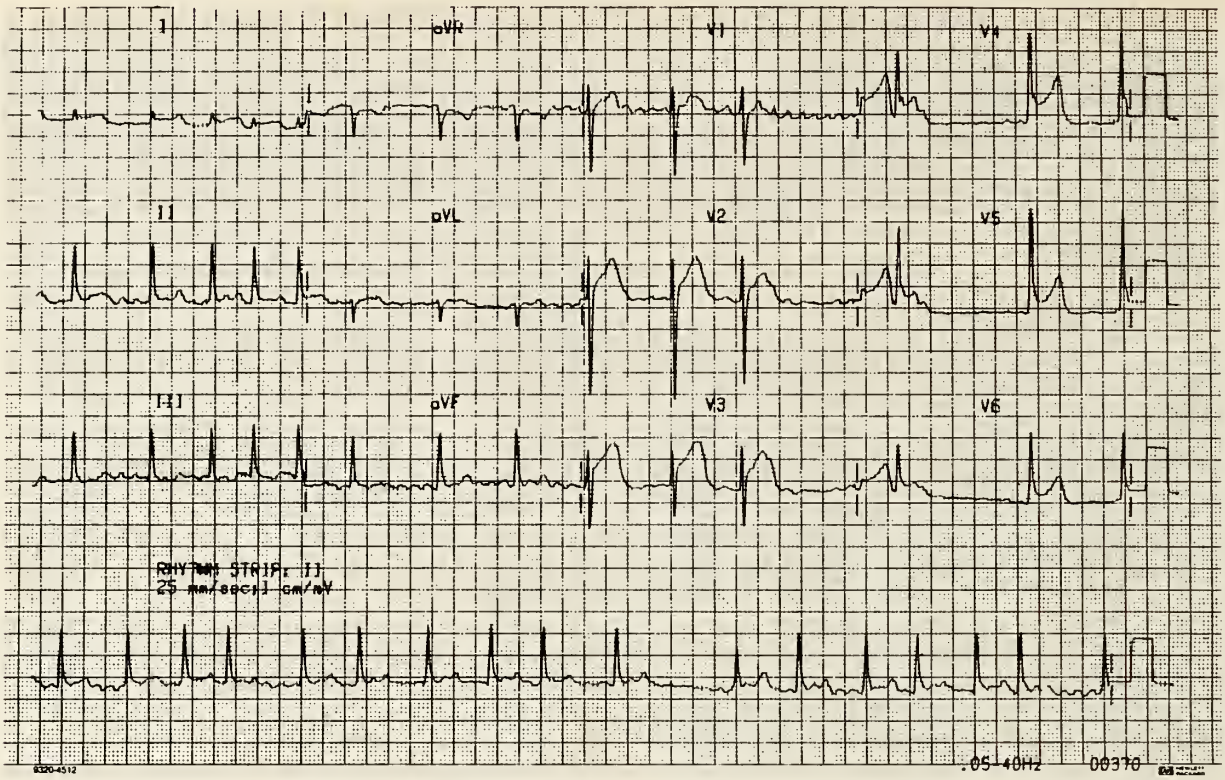

Figure 2.—Electrocardiogram on day 2 shows atrial fibrillation and concave ST-segment elevation in leads I, II, and V_2 to V_6, changes highly suggestive of pericardial inflammation.

The evanescence of heart block and its easy reversibility in most cases by administering atropine have previously been taken as evidence of a functional defect, rather than a structural lesion.[17] The bradyarrhythmias (complete AV block and prolonged ventricular asystole) in this patient, however, for which he was admitted to hospital and required temporary cardiac pacing, were more serious than the classic picture. This arrhythmic complication has not been reported previously and is highly suggestive of an organic involvement of conduction tissue by the acute rheumatic process.

Atrial fibrillation is thought to be a rare complication of acute rheumatic carditis, in contrast to its frequency in patients with longstanding mitral valvular disease with atrial enlargement and chronic atrial subendocardial inflammation.[18] This patient had episodes of tachyarrhythmia (atrial flutter and fibrillation) superimposed on a background of cardiac asystole and AV block without cardiac enlargement or cardiac decompensation. This suggests a direct atrial involvement. Aschoff bodies have been isolated in 21% to 55% of surgically excised left atrial appendages in patients with mitral stenosis.[19-20] The atrial tachyarrhythmias in this patient may relate to such pathologic abnormalities occurring in acute rheumatic carditis.

Acute rheumatic fever in the 1990s may differ from the classic patterns of the early 20th century.[11-14] More recent experience in Asian-Pacific regions and North America has revealed a lower incidence of carditis, erythema marginatum, chorea, and subcutaneous nodules but a higher incidence of polyarthritis and a higher proportion of adult patients. Acute rheumatic fever in adults recently has been characterized by dominant joint involvement while carditis, if present, is relatively mild.[11,12,14] My patient is unusual in that he presented with Stokes-Adams attacks as a result of his bradyarrhythmias. The underlying diagnosis of acute rheu-

TABLE 1.—*Progress of Patient With Acute Rheumatic Fever*

Date of Observation	*Fever*	*Arthritis*	*Cardiac Rhythm*	*Carditis*	*Erythrocyte Sedimentation Rate, mm/h*	*Antistreptolysin "O" titer, U/ml*
Day 1*	++	0	Complete heart block, supraventricular tachycardia	0	115	–
Day 3†	+	++	Atrial fibrillation	0	–	–
Day 5	+	+	Atrial fibrillation	Pericarditis	115	333
Day 10	0	0	Atrial fibrillation	Pericarditis	–	–
Day 20	0	0	Sinus	0	108	–
Day 30	0	0	Atrial fibrillation (intermittent)	0	55	–
Month 4	0	0	Atrial fibrillation (intermittent)	0	70	85
Month 6	0	0	Sinus	0	20-38	–

+ = mild intensity, ++ = moderate intensity, 0 = absent, – = not done

*Temporary cardiac pacing was performed on day 1.
†Treatment with rest and salicylate therapy was begun on day 3.

TABLE 2.—*Clinical Diagnosis of Acute Rheumatic Fever According to the Revised Janes' Criteria*

Revised Jones' Criteria	*This Patient*
Major	
Carditis	Pericarditis
Arthritis	Migratory polyarthritis
Erythema marginatum	Absent
Rheumatic nodule	Absent
Rheumatic chorea	Absent
Minor	
Fever	Low-grade fever
Prolonged PR interval in electrocardiogram	High-grade AV block
Leukocytosis	Present
High erythrocyte sedimentation rate	Erythrocyte sedimentation rate 110 mm/h
Previous rheumatic fever	Absent
Prerequisite	
Evidence of streptococcal infection	Antistreptolysin "0" titer 330 U/ml
Rheumatoid arthritis ruled out	Yes

AV = atrioventricular

matic fever with dominating carditis was confirmed by his subsequent development of polyarthritis and pericarditis. Such a combination of atrial fibrillation and AV block as a presentation of acute rheumatic fever has not been reported previously.

Bradytachyarrhythmias are encountered frequently in clinical practice, in particular among the geriatric population. Now that the medical community is facing a possible widespread return of rheumatic fever, this report highlights an atypical manifestation of the disorder and should alert clinicians to consider bradytachyarrhythmias as a presenting dominant manifestation of acute rheumatic carditis.

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Tularemia Presenting as an Isolated Pleural Effusion

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ALTHOUGH TULAREMIA has declined in incidence since it was first described by Edward Francis in 1925,[1] it continues to occur both sporadically and in epidemics in the United States.[2] There are several forms of tularemia, but it is the pneumonic form that is often mistaken for other, more common diseases. Because pulmonary tularemia is the most severe form, with the highest reported rates of mortality,[3] its recognition and treatment by physicians in and around endemic areas are important. We report a case of tularemia presenting as pleurisy in a young woman.

Report of a Case

The patient, a 37-year-old woman, was referred to the University of New Mexico Medical Center (Albuquerque) from her primary physician in southwestern Colorado, where she had been seen in mid-July 1991 with fever, chills, and pleuritic chest pain of two days' duration. Other presenting symptoms included diffuse myalgias, headache, night sweats, and a nonproductive cough. The results of chest

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x-ray films, a ventilation-perfusion lung scan, and initial laboratory tests, including rheumatoid and antinuclear antibody serologic tests, were unremarkable. Blood cultures and malaria smears were negative. Her symptoms persisted, and she was admitted to the University of New Mexico Hospital for further evaluation.

On admission to hospital ten days after presentation, the patient continued to have pleuritic pain, nonproductive cough, fever, and myalgias. She did not have any associated rash, insect bites, joint pain, or exposure to tuberculosis. Her medical history was unremarkable. She was married with two children; no family member had been ill. She worked extensively as a landscaper, and she admitted to having exposure to numerous animals at home, including a pet pig and a neighbor's dog that had recently become ill. She also had traveled in Honduras for ten days in May 1991 and there had mosquito bites.

On physical examination, she had a temperature of 39°C (102.2°F), a heart rate of 96 beats per minute, and a respiratory rate of 24. She was flushed and had bilateral cervical adenopathy. Her chest was dull to percussion in the left base, with decreased breath sounds and no rales, rhonchi, or wheezing. A radiograph of the chest revealed a left-sided free-flowing effusion with left hilar adenopathy and no associated infiltrate.

A diagnostic thoracentesis the next day yielded 20 ml of sanguineous fluid with 52 grams per liter (5.2 grams per dl) of protein, a lactate dehydrogenase level of 1,080 IU, glucose 30.5 mmol per liter (55 mg per dl), and a leukocyte count of 25.0×10^9 per liter (25,000 per μl), with 0.49 granulocytes and 0.48 lymphocytes. Serum values included a total protein of 71 grams per liter (7.1 grams per dl), with a peripheral blood leukocyte count of 10.6×10^9 per liter (10,600 per μl); 0.73 were granulocytes. A Gram's stain of the fluid did not reveal organisms, and initial cultures were negative. Skin tests were started for tuberculosis, and therapy with isoniazid, rifampin, and pyrazinamide was initiated. She became afebrile within 24 hours of starting therapy.

On July 30 a pleural biopsy was done using an Abrams' needle. Microscopic examination revealed fragments of skeletal muscle and fibrinopurulent exudate, with no organisms or granulomata identified. Acid-fast and periodic acid-Schiff–stained sections were negative for mycobacteria and fungi. Therapy was changed to rifampin, 600 mg a day orally, and doxycycline, 100 mg orally twice a day.

On August 1, *Francisella tularensis* was cultured incidentally from the pleural fluid that had been collected in standard aerobic blood culture bottles. A serologic test for *F tularensis* was done on a serum specimen from admission and was negative. A repeat titer done on August 7 yielded a positive result at 1:1,280. A *Brucella* titer on July 31 was positive at 1:40. She was treated for tularemia with streptomycin, 1 gram intramuscularly daily for 14 days, with resolution of her symptoms.

Interestingly, the neighbor's dog had a titer negative for *F tularensis* but was later diagnosed with systemic lupus erythematosus.

Discussion

In 1911 a new plague-like illness was discovered in squirrels by McCoy and Chapin while they were investigating outbreaks of bubonic plague after the 1906 San Francisco earthquake. The organism was isolated on a coagulated egg medium and named *Bacterium tularense* after Tulare County, California, the site of the discovery.[4] The first bacteriologically confirmed human case of infection was described by Wherry and Lamb in 1914.[2] Francis followed with seven more cases in 1921. In 1928, drawing on his experience with more than 800 cases, Francis summarized the clinical and epidemiologic features of the disease. In 1959 the genus name of the organism was changed to *Francisella* in recognition of the major contributions he had made to the study of tularemia.

Several clinical forms of the disease have been described, based on the portal of entry. Lymph node involvement is uniformly present. Most commonly, a primary ulcer is found on the skin (ulceroglandular), in the eye (oculoglandular), or in the nasopharynx (oropharyngeal). Lymphadenopathy can occur without a recognizable cutaneous ulcer (glandular). Infection is often localized in these forms, but more disseminated disease can occur as a result of bacteremia. Systemic illness is much more common when the organism enters through the gastrointestinal tract (typhoidal) or the lungs (pneumonic).

Tularemia presenting as pleurisy and pleural effusion without pneumonia is uncommon. Pleural effusion is much more likely to occur when parenchymal abnormalities are present and has been reported in as many as 82% of cases with pneumonia.[5,6] The incidence of pleural effusion increases as untreated disease progresses, but it has been found as early as three days after the onset of symptoms and is often bilateral.[7,8] Pleural effusions caused by *F tularensis* have characteristically been exudates, with protein values as high as 62 grams per liter and leukocyte counts that range from 6.3 to 16.0×10^9 per liter.[2] Although lymphocytic-predominant fluid does occur, most earlier reports suggest that granulocytic predominance is more common.[9,10] The fluid can be turbid or serosanguineous.

Working with cultures of *F tularensis* is hazardous to laboratory personnel[3] because the organisms are easily aerosolized and inhaled, placing workers at risk for the illness developing. In addition, culture of the organism requires special media; therefore, directed cultures of pleural fluid are rarely done. *F tularensis* has been recovered from pleural fluid by direct culture,[11] but this is decidedly rare. *F tularensis* does not stain well with Gram's stain, and the demonstration of the organism in pleural fluid by this method has not been reported.

Serologic tests are used to diagnose tularemia. A titer of 1:160 is presumed diagnostic.[2] This value is somewhat arbitrary as there have been no studies that correlate culture-proven natural infections with antibody titers. Most titers are diagnostic within 10 to 14 days after presumed exposure; however, laboratory studies of volunteers using killed vaccine found that diagnostic titers were not achieved until the third week of illness.[12] Follow-up serologic titers often remain mildly elevated for years.[12]

Tularemia infection may stimulate antibodies to *Brucella* species through antigenic cross-reactivity. This is especially the case if the tularemia titer is greater than 1:320. Conversely, patients with brucellosis may have elevations in their tularemia titers.[13] As our patient showed, this serologic cross-reactivity can lead to confusion regarding the correct diagnosis.

Our patient likely acquired her infection from the bite of a deer fly during the course of her landscaping work. Although

rabbits have classically been linked to the illness, arthropod-borne illness is becoming more common, with ticks being the principal reservoir.[2] Rabbits and other mammals represent a source of infection, particularly in the winter months; these animals rarely represent true reservoirs, however, because most infected mammals either become sick and die or recover with loss of the organism.[1] Although little is known about the actual arthropod infection, it is thought that transovarial transmission occurs. Ticks may live as long as 21 years, with great potential for harboring the organism.[14(pp227,323)] The organism has been identified in more than 55 different arthropods. Francis was the first to describe cases of tularemia caused by the deer fly. The disease had popularly been known as "deer fly fever," with a predominance noted in the Western states of Utah and Colorado and an associated peak incidence in the summer months. Typical of arthropod-borne infections, a definite source of infection is often not identified, as in our case.

Streptomycin is the drug of choice in tularemia. In vitro it is both bacteriostatic and bactericidal. Patients treated with streptomycin generally defervesce in 48 hours and require only one 14-day course of therapy. Gentamicin, tetracycline, and erythromycin have been used with only varying success.[2] It was of interest that our patient's fever resolved within 24 hours of the start of therapy with rifampin.

Tularemia continues to present a diagnostic challenge to physicians in and around endemic areas. An understanding of its protean manifestations is essential in its recognition and appropriate treatment. In our case, tularemia presented as pleurisy with a pleural effusion. Although isolated pleural effusion with associated pleuritic pain is often self-limited and presumed viral in origin, we suggest that tularemia be considered in those patients whose illness fails to resolve in a timely manner. Serologic tests are diagnostic, and a rapid clinical response can be expected with streptomycin therapy.

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Medicolegal Complications of Postpartum Catatonia

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SINCE PRE-REVOLUTIONARY times and with the adoption from England of the mandate of *parens patriae*, protecting severely impaired mentally ill persons has been the responsibility of the state. This mandate calls for protecting all citizens or subjects unable to protect themselves, such as minors or the insane. To fulfill its social objectives and to protect the mentally ill from the abandonment and despair common before the development of modern psychiatric institutions, the state charged the medical and psychiatric community with responsibility for the care and treatment of the individual. Concomitantly, the legal community developed laws ensuring guardianship of the insane and incompetent. This partnership of care reached its zenith in the late 1960s with the crafting of laws such as the Lanterman-Petris Short Act of California, which weighed the medical care and the legal protection needs of the mentally ill, in an attempt to balance requirements and rights in a humane fashion.

The Lanterman-Petris Short Act of California mandated the formation of an office of patients' rights advocacy. Among the many responsibilities defined under the California Welfare and Institution Code, Section 5500(a), patient advocacy for the mentally ill was "to protect their rights or to secure or upgrade treatment or other services to which they are entitled." An advocate's role in practice occurs in adversarial-type hearings with an attorney sitting in lieu of a judge. In the hearings, a patient's rights advocate protects the patient from the physician, who attempts to retain and treat the patient.

The individual rights movement in the 1970s gave rise to a phenomenon that can best be described as distrust of the professional community. The field of psychiatry, which for a number of years had been retreating from ascribing a medical basis to psychiatric illness, was undermined further by prominent psychiatrists who perceived mental illness or psychosis as a myth or adaptation rather than an illness, advancing the perception of medical psychiatry as an instrument of abuse rather than treatment. Fostered by this distrust, a series of legal decisions and laws closely regulated care through the courts, exemplified by legislation restricting the use of electroconvulsive therapy.

More recently, the decision in *Riese v St Mary's Hospital* separated involuntary admission to hospital from involuntary treatment with antipsychotic medications.[1] Under this decision, these medications can be given to nonvoluntary patients only after a separate judicial hearing. In the two years since the *Riese v St Mary's Hospital* decision, we have become aware of its devastating consequences.

Report of a Case

The patient, a 22-year-old woman with no previous psychiatric history, was admitted to a psychiatric service ten days

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after a cesarean section. Her family noticed that shortly after delivery she was fearful, acted bizarre, and had a personality change accompanied by delusional thinking. She began to believe that she was a psychic and was able to read people's minds. This personality change was associated with severe mood swings. She displayed little interest in caring for her newborn child and had difficulty concentrating. On the urging of her family, the patient admitted herself voluntarily to the psychiatric service.

On admission she was floridly psychotic and had a temperature of 38.3°C (101°F). The fever was thought to be from either an upper respiratory tract or a urinary tract infection. She was diagnosed with an affective disorder, and treatment was begun with lithium carbonate and perphenazine. Three days after admission, she became agitated, more labile and delusional, and no longer cooperated with care. The dose of perphenazine was increased, lorazepam was added to the regimen, and almost continuous physical restraints were needed. She required special nursing. To continue treatment, the law required that a judicial hearing be held to determine if the severity of her clinical state permitted the patient to be held against her will, as well as a second and separate *Riese* hearing to determine if she was being treated against her will.

California law permits initial involuntary treatment without a hearing during the first 72 hours of evaluation and hospital stay. While awaiting the hearing, treatment was continued. Five days after admission, a hearing was convened. A hearing officer-lawyer appointed by the court heard the case and deemed the patient "gravely disabled" and thus holdable. The patient was held involuntarily under Section 5250 of the Welfare and Institution Code of California.

Immediately after the first hearing, a second hearing was convened to determine if the patient could be treated involuntarily with medicine. A number of professionals were involved in the hearing, including an attorney acting in lieu of a judge (judge pro tem), one appointed by the court to represent the patient, another retained by the hospital, a patients' rights advocate retained by the county, and the psychiatrist presenting the case.

The court-appointed attorney requested a brain scan and raised the possibility of a brain hemorrhage at the time of delivery. The judge pro tem denied permission to administer medication involuntarily and ordered that the patient be given medication only when and if she wanted it. As a result of this hearing, the systematic treatment with psychotropic medication was stopped on the sixth day of the patient's hospital stay.

From this day onward, unable to treat effectively, physicians were able to maintain hydration only through the use of intravenous fluids and four-point physical restraints. The patient was unwilling to eat and lost weight. Increasingly agitated, she was given fluphenazine hydrochloride, which was administered only when she accepted it. By the tenth day she had a creatine kinase level of 876 units per liter and a pulse rate of 120 beats per minute, which accompanied the unremitting fever. She remained unresponsive to antipsychotic medication. As a result of concern over the possible development of a neuroleptic malignant syndrome, on the tenth day all psychotropic drugs were stopped. A neurology consultation was requested, and an electroencephalogram was normal. The neurologist found no evidence of the neuroleptic malignant syndrome. With no one able to make treatment decisions regarding her health, a petition was prepared requesting the county to appoint a temporary conservator.

The patient continued to express paranoid delusions, threatened to harm others, and was increasingly aggressive. The results of a lumbar puncture study were normal. On the 15th day, as a result of her continuing refusal of food and water, increasing agitation and the constant need for four-point restraints, and an unabated psychosis unresponsive to medication, she was treated more aggressively with neuroleptic drugs and lorazepam, with little clinical change. By the 21st day of her hospital stay, with continuing hyperthermia and still unresponsive to medication, the patient's creatine kinase level had risen to 1,339 units per liter. All medication was stopped again because of the fear of neuroleptic malignant syndrome. Symptoms of waxy flexibility, excessive posturing, and negativism were also developing. After a ten-day delay, a conservator had been appointed, and, 23 days after admission, the conservator gave permission to do a brain scan. The patient's agitation required that she be given nitrous oxide anesthesia to do the scan. The patient's county-appointed attorney objected to the procedure because he considered the intended use of the nitrous oxide anesthesia to be invasive. He appealed to the county mental health director to overrule the district attorney and block the procedure, demanding that the case be sent to court so that a superior court judge could decide whether the patient would undergo the procedure. It took four days to obtain a court hearing. With no clinical evidence presented to support the objections to the procedure, the judge gave permission to proceed. On the 27th day of her hospital course, the scan was done; it revealed no pertinent information.

On the 24th day of her hospital stay, a decision was made to proceed with electroconvulsive treatment. Under California law, this is permitted in a nonvoluntary patient only after all other possible treatment has been tried. The patient's waxy flexibility continued, now accompanied by a scissorslike crossing of the legs and fingers associated with other symptoms, such as auditory and visual hallucinations. The diagnosis of lethal catatonia was made.[2,3] As mandated by law, the treating psychiatrist obtained three psychiatric consultants, adding another two days of delay. Each filled out the necessary affidavits, and permission was requested of the conservator. A fifth psychiatrist, appointed by the county, was now required to review the first four opinions, and this added another day of delay.

The case was again referred to the superior court judge for permission to proceed. The court advised that it would take ten days for a hearing. The physicians were concerned that the patient was dying. Consequently, a letter was hand-delivered to the court explaining the urgency. Even so, intervention by the hospital attorney was necessary to speed the legal timetable, and a hearing was held on the patient's 32nd day of hospital stay. With no clinical evidence to the contrary, the judge ruled in favor of the requested treatment on a Friday afternoon. On Saturday morning, the 33rd day of her hospital stay, electroconvulsive therapy was done.

Within 36 hours, the patient no longer required nasogastric feedings, intravenous fluids, or restraints. Special nursing care was stopped. The patient was sociable and began to feed herself voluntarily. An uneventful course of electroconvulsive treatment followed, and the patient was discharged.

Discussion

Legal procedures posed a serious obstacle to caring for this patient and resulted in notable delays in treatment. Al-

though intended to protect the patient's civil rights, the net effect was just the opposite. Because her physicians had to use physical restraints and extraordinary measures to maintain life, the patient was denied the right to be free of a threat to life and the right to be free of physical restraint. Without the legal obstacles, she could have been treated effectively in 14 days, sparing her weeks of additional involuntary detention and restraint and without her life being in danger.

Because of legal obstacles, costs increased. Our patient required 30 days of special 24-hour nursing, 23 days of parenteral hydration, 8 days of nasogastric feeding, and 18 additional hospital days while awaiting the results of legal proceedings. These hearings were directed exclusively at procedural legal matters. At no point was medical evidence introduced to alter the treatment plan. The county bore the cost of a patients' rights officer, a hearing officer, and the fees for the electroconvulsive therapy proceedings. The family paid their own attorney, and the physicians were denied all payment for the care they provided. Most of these expenses were billed to the state mental health budget in California.

Our case is an example of how using an adversarial system for making psychiatric care decisions does not help the patient. At the core is the issue of assuming responsibility for a mentally ill patient when that person is incompetent. Although traditionally the family, together with the physician, was trusted to make decisions, the family now is largely excluded. Physicians are still expected to care for and cure, but they are denied the power to make clinical decisions. Bureaucrats and lawyers divide up the clinical decision making, but they are not responsible for their actions, with the exception of the conservator, who also is denied decision-making power. This power is left to the crowded courts.

Many reforms are necessary, but any changes must fulfill basic principles. No legal procedure should endanger a patient's life, extend the time a patient remains in hospital or in restraints, delay appropriate care, or increase medical costs. Several basic remedies to the present set of procedures are in order. Primarily, the concept of "danger to self, others," and "gravely disabled" includes a vague set of criteria useful only as a screening tool. These criteria should be abandoned at the time of a hearing. What is of concern is whether or not persons suffer such impaired mental processes that they can no longer act cogently and responsibly on their own behalf. For this they must be sufficiently free of disordered thought and possess the free will and information necessary to make rational decisions. When these are absent or sufficiently impaired so as to render patients incapable of adequately assuming responsibility and representing themselves, the state has an obligation to intervene.

Once the state has determined that a patient is impaired, the decision-making function must be assumed by a state-appointed patient conservator or advocate. This advocate must be responsible for the total mandate of Section 5500(a), including "securing or upgrading treatment or other services to which the patient is entitled." One right should not be permitted to overshadow any other rights. For this purpose, the findings of an involuntary hearing and of the *Riese* hearing must be combined into one. This hearing should occur within 12 hours of notifying the court. The appointed advocate should be responsible to the patient and the family for assuring speedy, humane, and appropriate medical care when indicated under the least restrictive conditions, acting as a highly educated, informed parent or concerned family member might act under the doctrine of *parens patriae*. This person should be skilled in medical psychiatry as well as in the legal issues that affect patients' welfare.

The budget for legal matters and the costs incurred arising from these must be stripped out of the mental health budget and separately budgeted by the legislature. To include these expenses in the health budget, as is currently done, is to falsely inflate the health budget and subsequently deny medical care to patients.

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Temperate Zone Pyomyositis

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PYOMYOSITIS is a primary bacterial infection occurring in skeletal muscle with no obvious local or adjacent source of infection. It is frequently called tropical myositis because of its high incidence in warm, humid climates. It is responsible for as many as 4% of hospital surgical admissions in East Africa.[1] The first series was recorded in 1885 by Scriba.[2] The first case reported in the United States was in 1904.[3] An additional 93 cases have been described in North America, all since 1971. The early cases occurred mostly in healthy children and were reported mainly from hot, low-lying areas. Patients recently reported in the literature have often had an underlying disorder resulting in immune suppression, such as hematologic disease,[4-8] human immunodeficiency virus (HIV) infection,[9-13] connective tissue disorders,[7,14-16] and transplantation.[17]

We report our experience with 14 patients in Oregon over the past ten years.

Patients and Methods

Patients were identified by a computer search of hospital admission records or by direct review of the records of the infectious disease consulting service from 1979 to 1990. The search terms used were pyomyositis, myositis, muscle infection, and soft tissue infection. About 200 patient records were reviewed.

In all the cases included in this study, pyomyositis was

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confirmed at surgical exploration. Cases were excluded if soft tissue infection did not involve muscle, muscle infection was by direct extension from nonmuscle tissue, or insufficient information was available for a definite diagnosis. Patients with psoas muscle involvement were excluded if there was a history of a urinary tract infection.

All data were obtained from patient medical records. One case (patient 4) had previously been reported,[6] and another patient (No. 13) received definitive treatment at Ralph K. Davies Medical Center, San Francisco, California.

Results

Patients ranged in age from 15 to 70 with a mean of 43 years. Of the 14 patients, 8 were men (Table 1). Only two patients had no associated illness or antecedent trauma; four patients had one possible risk factor or source of infection, and the other eight had two or more of these factors. None had recently traveled to the tropics.

Four patients had an underlying hematologic disease, three had had minor trauma, and two had diabetes mellitus. Both patients previously treated with corticosteroids had an additional possible risk factor: systemic lupus erythematosus in one and atopic dermatitis in the other. One patient had HIV infection.

No source of infection was found in eight patients, and a possible source was determined in six. This infection was often temporally remote; four patients had had cellulitis diagnosed a month earlier, and one had gingivitis three months before the development of pyomyositis. In three of the patients, cellulitis overlay the muscle in which pyomyositis developed.

The duration of symptoms before hospital admission varied from 1 to 70 days (mean 17 days). The chief symptom in all patients was pain in the involved muscle. Clinical signs varied depending on the site of the abscess. One of the patients with pyomyositis in a psoas muscle had no external localizing signs. Local tenderness was noted in all of the other patients, with swelling in 12 and erythema in 9. Fluctuance was found in three patients.

A single muscle was infected in 12, two muscles in 1, and 1 patient had three involved muscles. The large trunk and thigh muscles were most commonly affected, but calf, upper arm, and forearm muscles were occasionally the site of abscess formation.

TABLE 1.—*Demography, Medical Background, and Possible Source of Infection in 14 Patients With Pyomyositis*

Patient	Age, yrs	Sex	Site	Associated Illness	Possible Source of Infection
1	42	♂	Buttock	Previous corticosteroid use, atopic dermatitis	Dermatitis
2	33	♂	Buttock	Past intravenous drug abuse	Skin needle tracks and abrasion, lymphadenitis
3	31	♀	Thigh, upper arm	SLE, past cyclophosphamide and corticosteroid therapy	Unknown
4	66	♂	Thigh	Diabetes; preleukemia	Cellulitis 1 mo before
5	57	♀	Calf	Minor trauma	Unknown
6	19	♂	Psoas	None	Unknown
7	15	♀	Thigh	None	Unknown
8	66	♀	Calf	Diabetes, minor trauma	Cellulitis 1 mo before
9	70	♂	Psoas	Myelodysplasia, bladder carcinoma	Unknown
10	47	♂	Thigh	Anemia, minor trauma, hematuria	Cellulitis 1 mo before, gingivitis 3 mo before
11	30	♀	Psoas, thigh, buttock	Paraplegia, postpartum	Unknown
12	25	♂	Forearm	Previous bone fracture	Unknown
13	34	♂	Thigh	HIV infection	Cellulitis 3 wk before
14	70	♀	Thigh	Aplastic anemia	Unknown

HIV = human immunodeficiency virus, SLE = systemic lupus erythematosus

TABLE 2.—*Laboratory Investigations in 14 Patients with Pyomyositis*

Patient	Leukocyte Count, x 10^9/liter*	Neutrophil Count†	Band Forms†	ESR, mm/h‡	Blood Culture Results	
					Positive	Organism
1	14.4	0.71	0.08	105	Yes	*Staphylococcus aureus*
2	14.4	0.48	0.25	--	Yes	*S. aureus*
3	7.0	0.74	0.05	--	No	*S. aureus*
4	0.7	0.20	0.12	138	No	*S. aureus*
5	29.8	0.86	0.16	--	Yes	*S. aureus*
6	19.9	0.82	0.04	76	Yes	*S. aureus*
7	13.2	0.60	0.21	108	No	*S. aureus*
8	12.3	0.86	0.02	>140	No	*Escherichia coli*
9	7.2	0.52	0.03	80	No	*S. aureus*
10	26.8	0.71	0.18	94	No	*Streptococcus intermedius*
11	17.7	0.77	0.13	116	Yes	*S. aureus*
12	7.5	--	--	48	No	*S. aureus*
13	3.8	0.78	0.01	56	No	*S. aureus*
14	1.0	0.29	0.18	--	No	*S. aureus*

ESR = erythrocyte sedimentation rate

*Values expressed in Système International units. For conventional units (cells/μl), multiply by 1,000.
†Expressed as a fraction of 1.
‡Westergren method.

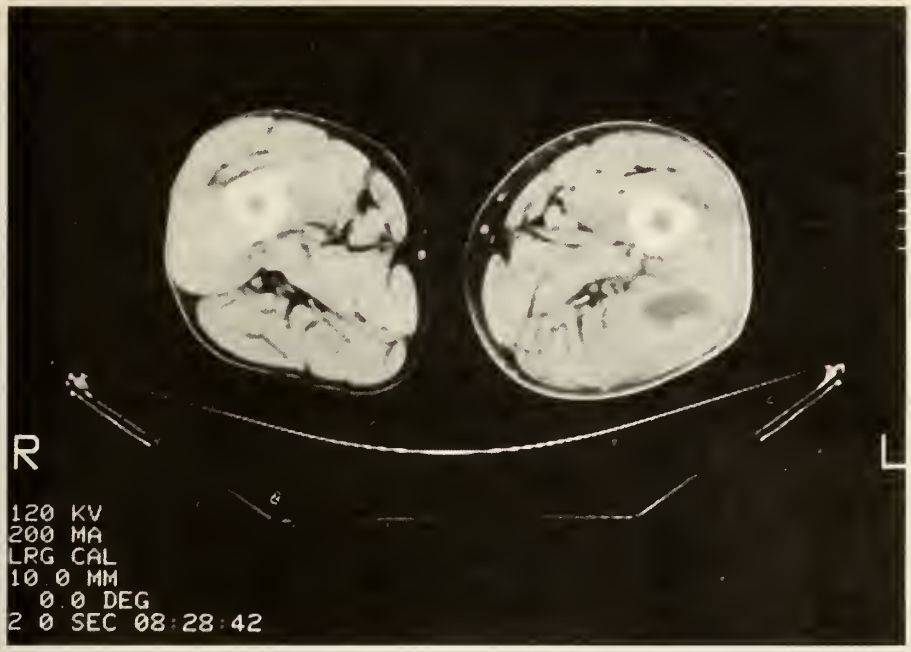

Figure 1.—A computed tomographic scan shows pyomyositis in the long head of the left biceps femoris (patient 4).

Laboratory Results

Leukocyte counts at admission in patients without hematologic disease or HIV infection varied from 7.0 to 29.8×10^9 per liter (7,000 to 29,800 cells per μl) (mean 15.1 ± 6.9) with a predominance of neutrophils and neutrophil precursors in all cases (Table 2). The erythrocyte sedimentation rate (Westergren method) was measured in ten patients and was invariably raised, ranging from 48 to more than 140 mm per hour (mean 96 ± 31). It was greater than 100 mm per hour in six (43%) patients.

An organism was cultured from a muscle or blood specimen in all patients. *Staphylococcus aureus* was the bacterium isolated in 12 (86%), *Escherichia coli* in 1 (7%), and *Streptococcus intermedius* in 1 (7%) subject. Blood cultures were positive for *S aureus* in 5 of 14 patients.

Radiology

Imaging techniques were used in 13 patients. Computed tomographic scanning was used in eight patients and in each case localized the disease process correctly to the involved muscles. The findings were not specific for pyomyositis, however. Descriptive terms used include abscess, fluid collection, low attenuation uptake, ring-enhancing lesion (Figure 1), and diffuse uptake. Computed tomographic scanning guided aspiration in three cases.

Scintigraphy—scanning using gallium 67, technetium Tc 99m, or leukocytes labeled with indium 111—was done in ten patients. It indicated soft tissue uptake in six patients, was falsely positive for osteomyelitis in two, and helped diagnose a secondary complicating osteomyelitis in two. Ultrasonography suggested pyomyositis in four and guided aspiration in one patient.

Differential Diagnosis and Treatment

A number of diagnoses were considered at presentation (Table 3). Cellulitis (8 patients [57%]), osteomyelitis (3 patients [21%]), and hematoma (3 patients [21%]) were considered most commonly, and deep vein thrombosis, perinephric abscess, and muscle strain were occasionally mentioned. The correct diagnosis was considered early in the disease course in only one patient (7%). After hospital admission, there was a delay to definitive treatment (incision and drainage of abscess) of longer than three days in nine patients (64%). As a result, prolonged hospital stays were the rule, with a mean of 28 ± 15 days. Some patients in whom the diagnosis was made early still had prolonged hospital stays. Serious complications developed in nine patients (64%), including osteomyelitis (3), multiorgan failure due to sepsis (3), and death in two patients (14%). Bacteremia occurred in five patients (36%), and all bacteremic patients suffered disease complications. Neither of the patients who died had positive blood cultures on presentation, however. The mean duration of hospital stay of the patients with bacteremia (34 ± 16 days) was longer than that of the patients who did not have bacteremia (21 ± 12 days). Preexisting illness or predisposing factors appeared to influence the outcome. Both patients who died had serious underlying diseases; one had myelodysplasia, and the other suffered from aplastic anemia. Both had gram-negative bacteremia before death; *S aureus* had been identified in the muscle tissue.

Discussion

Muscle is remarkably resistant to infection. Muscle trauma is necessary before experimentally induced bacteremia causes pyomyositis in animals.[18] In humans, muscle abscess is rarely a complication of severe staphylococcal sepsis.[19] Pyomyositis has been considered primarily a tropical disease that occurs mainly in young and relatively healthy persons. Several unproven hypotheses have been proposed to explain these demographics, including malnutrition,[20,21] previous protozoal[22,23] or viral muscle infection,[24] and disordered immunity.[25,26]

Our series of patients adds to the reported experience from temperate zones over the past five years and reveals different demographic features. Patients with temperate zone pyomyositis are generally older than those reported from the tropics and in early reports from the US. Furthermore, most of the recent patients have had an associated underlying con-

TABLE 3.—*Initiol Diagnosis ond Treotment Result in Patients With Pyomyositis*

Patient	Initial Diagnosis	Delay to Drainage, d	Hospitol Stoy, d	Complications
1.....	Cellulitis	10	27	Osteomyelitis
2.....	Myositis	1	47	Multiorgan failure
3.....	Fasciitis, cellulitis	1	8	None
4.....	Cellulitis, Sweet's syndrome	28	39	None
5.....	Thrombophlebitis, cellulitis, deep venous thrombosis	6	34	Multiorgan failure
6.....	Retroperitoneal hematoma, appendicitis	8	10	Abnormal results of liver blood tests
7.....	Spontaneous hematoma	1	14	None
8.....	Cellulitis, deep venous thrombosis	3	21	None
9.....	Osteomyelitis, perinephric abscess	20	42	Secondary *Escherichia coli* infection, ischemic bowel disease, death
10.....	Herniated disc, cellulitis, osteomyelitis	32	10	Osteomyelitis
11.....	Perinephric abscess, SBE	10	51	Septic trochanteric bursitis, osteomyelitis
12.....	Osteomyelitis, cellulitis	2	14	None
13.....	Cellulitis, lymphoma, muscle strain	78	28	Repeated drainage × 4
14.....	Pyomyositis, muscle strain, hematoma	14	42	Gram-negative bacteremia, multiorgan failure, death

SBE = subacute bacterial endocarditis

dition—including diabetes,[27-30] hematologic disorders,[4-8] connective tissue disease,[7,14-16] and HIV infection[9-13]—that may make their muscle tissue more susceptible to bacterial infection. The age distribution of our series is broad (15 to 70 years), but 11 (79%) of the patients were 30 years of age or older.

Twelve (86%) of our patients had underlying conditions that may have predisposed them to the development of pyomyositis. These factors include minor trauma, an associated illness, or a possible source of infection. Conditions such as diabetes mellitus, blood dyscrasias, and immunodeficiency represent additional risk factors for the development of pyomyositis in temperate areas.

Despite different demographic features, the muscles involved in our series are similar to those in tropical cases. Truncal and proximal large lower limb muscles were most commonly involved. Likewise, the most usual organism was *S aureus.*

Clinical and laboratory features of our series were similar to those described in the literature. In a few recent case reports,[14,15,31] magnetic resonance imaging has been found to be more sensitive than computed tomographic scanning, but it was not used in our patients.

Pyomyositis is relatively uncommon in temperate climates and is often considered late in a diagnostic workup. The differential diagnosis depends on the site involved and includes deep vein thrombosis, cellulitis, osteomyelitis, and soft tissue malignancy. Cellulitis was the most frequently considered diagnosis in our series, consistent with the observation that erythema overlying the affected muscle was noted in most of the cases. A high index of suspicion for pyomyositis needs to be maintained in patients presenting with symptoms suggestive of more common illnesses, especially when diagnostic studies are nonconfirmatory or when the response to treatment is inadequate. Substantial delays in reaching the correct diagnosis are common and may have contributed to prolonged hospital stays in our patients. The mortality rate of 14% in this series is probably a reflection of serious underlying disease in many of the patients.

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Pulmonary Paragonimiasis in Southeast Asians Living in the Central San Joaquin Valley

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HUMAN PARAGONIMIASIS is caused by the lung fluke *Paragonimus westermani* and other species. This parasite is endemic in the Far East, especially in areas of central China, Japan, Korea, the Philippines, and Southeast Asia (Vietnam, Laos, Cambodia, Thailand).[1] The disease is also found in Central and South America, West Africa, and the Indian subcontinent. Its occurrence in the United States is rare.

The central portion of California's San Joaquin Valley has had a large influx of refugees from Southeast Asia. As of 1988, an estimated 48,000 persons had emigrated to the counties of Merced, Madera, Fresno, Kings, and Tulare (*Estimates of Refugees in California Counties and the State: 1988,* Report SR 88-1 [January 1990], Department of Social Services, County of Fresno, California, pp 8-9). This population is now thought to exceed 60,000, of which about 49,000 are living in the Fresno County area (*Fresno County Plan for Refugee Services*—1990, Department of Social Services, County of Fresno, California, p 5). Heretofore, no cases of paragonimiasis from the Central Valley have been reported to the state health department (Terry Thompson and Edward Graham, PhD, MPH, Department of Health Services, State of California, oral communication, December 1990). Therefore, we report the following four cases documented within this population. In addition, we review the life cycle and human pathogenesis of this parasite.

(Yee B, Hsu JI, Favour CB, Lohne E: Pulmonary paragonimiasis in Southeast Asians living in the central San Joaquin Valley. West J Med 1992 Apr; 156:423-425)

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Report of Cases

Patient 1

The patient, a 39-year-old Laotian man, presented to a local hospital in Merced, California, in January 1979 because of persistent hemoptysis. When he was a fighter pilot in 1968, he was shot in the chest, resulting in hemoptysis. After chest tube placement, he did well except for infrequent episodes of hemoptysis over an 11-year period, for which he received penicillin shots. He became a United States resident in 1977.

On physical examination, the patient had scars from the gunshot wound at the right upper anterior chest and the chest tube site on the back. He had a leukocyte count of 11×10^9 per liter (11,000 per μl) with 0.06 eosinophils. A recent purified protein-derivative (PPD) skin test measured 14 mm. Chest x-ray films showed minimal fibrosis in the right upper lobe, attributed to the old gunshot wound, and shifting cystic opacifications in both upper lobes. Several sputum specimens were negative for acid-fast bacilli.

Based on the significant PPD reaction, a regimen of isoniazid, 300 mg a day, was started. After three months of isoniazid therapy, the patient stopped the medication on his own because of side effects. He continued to have hemoptysis. Bronchoscopy was unrevealing. Serologic tests for coccidioidomycosis were negative. A sputum test for ova and parasites was positive for *Paragonimus* species. A complement fixation titer for *P westermani* was positive at 1:128. The patient was given bithionol, 30 mg per kg of body weight every other day for three to four weeks. He reportedly took some of the medication as prescribed, and the hemoptysis had ceased when he was seen several months later. The patient has since been lost to follow-up.

Patient 2

The patient, a 13-year-old Laotian boy, was seen at a local community hospital in February 1984 because for the past three days he had had fever, chills, and hemoptysis. He had been in the United States for two years. While living in Laos, he had had bouts of hemoptysis since age 7. After drinking a home remedy, he purportedly stopped coughing blood within three days. Years later, his hemoptysis recurred while he was in Thailand. He reports being treated with some antituberculous medication for several months. He remained in good health until his current illness.

On physical examination, coarse rhonchi were heard over the right anterior portions of his chest. The patient's leukocyte count was 6.1×10^9 per liter (6,100 per μl) with 0.05 eosinophils. Other laboratory values were within normal limits. A chest radiograph revealed a few cystic areas in the right lower, right upper, and left upper lobes. A presumptive diagnosis of pulmonary tuberculosis was made, and the patient was sent to the Fresno County Public Health Department for further workup. Skin tests for PPD and coccidioidomycosis were negative. Culture of several sputum specimens for acid-fast bacilli and fungi was negative. A sputum test for ova revealed *P westermani.*

The patient was treated with praziquantel, 25 mg per kg three times a day for one day. He was seen three weeks later with the report that his hemoptysis had resolved. Tests of sputum were negative for ova. A second chest radiograph showed no substantial change. He has remained well in follow-up to the present.

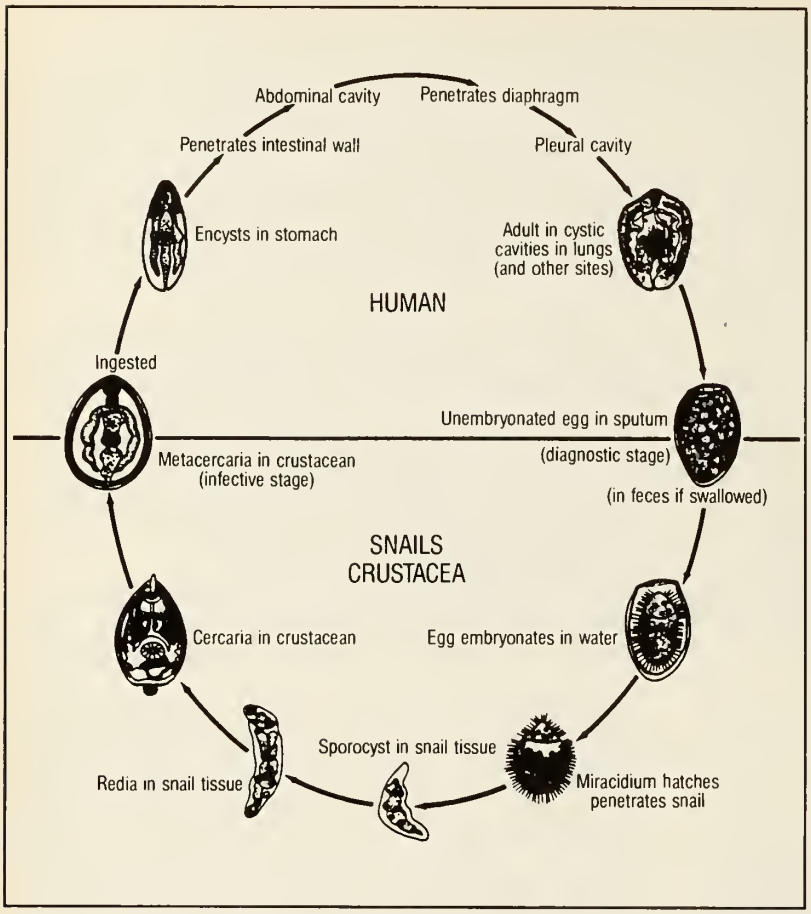

Figure 1.—The life cycle of the trematode *Paragonimus westermani* is shown (from the Centers for Disease Control, Atlanta, Georgia).

Patient 3

The patient, a 20-year-old Laotian man, was seen at a local public health clinic in September 1988 because of hemoptysis, having emigrated to the United States a year before his presentation. A physical examination revealed scattered inspiratory crackles at the right base of his chest. A chest radiograph showed an infiltrate in the right middle lobe. A PPD skin test measured 10 mm. Several sputum smears and cultures for acid-fast bacilli were negative. A diagnosis of active tuberculosis was made, and he was treated with a regimen of isoniazid, rifampin, and pyrazinamide.

In December 1988, the patient was seen at the neurology clinic at Valley Medical Center in Fresno complaining of vertigo. There was a questionable history of seizures over the past four to five years, but an extensive neurologic workup was negative. His antituberculous regimen was stopped after five months because of the vertigo. He returned to the medicine clinic at Valley Medical Center in April 1989. His dizziness had resolved; his episodes of hemoptysis persisted. Serial chest radiographs showed no changes; the right middle lobe infiltrate was considered to be a chronic interstitial process. On testing both sputum and stool specimens for ova and parasites, the sputum was found to harbor *P westermani*. The patient was given praziquantel, 25 mg per kg three times a day for one day. He tolerated the medication well and returned four weeks later having no more hemoptysis. Retesting the sputum for ova and parasites was negative.

Patient 4

A 40-year-old Thai woman was seen at the Merced County Health Department in February 1991 for refugee screening within a month after she arrived in the United States. She had had intermittent hemoptysis for the past four years. In Thailand her symptoms were attributed to tuberculosis. She was treated with isoniazid, rifampin, ethambutol hydrochloride, and pyrazinamide. The pyrazinamide was given for two months, and the other medicines were continued for a year. Despite her compliance in treatment, intermittent hemoptysis continued.

On physical examination, the patient had scars from an old bullet wound entering the posterior right side of her chest, with multiple exit sites under her right breast. The chest was clear to auscultation. A chest radiograph showed infiltrates bilaterally in the middle and lower lung fields. A density in the left lower lung field appeared to have a central air-fluid level. A PPD skin test was negative. Two sputum smears for acid-fast bacilli were negative. Paragonimiasis was suspected on the basis of a nonsignificant PPD test, continued hemoptysis, and persistent abnormal x-ray findings despite an adequate course of supervised antituberculous treatment. A sputum test for ova and parasites revealed *P westermani*. The patient was given praziquantel, 25 mg per kg three times a day for two days. At follow-up visits over the next two months, the hemoptysis had stopped. The infiltrates and possible cavitary lesion had cleared.

Discussion

A history of shellfish or raw crab ingestion was later confirmed in the first three patients. The fourth patient gave a history of making salads with watercress taken from the local rivers in Southeast Asia. Each patient had been treated for tuberculosis without resolving either their hemoptysis or

their pulmonary infiltrates. In none of these patients were sputum studies positive for tuberculosis. The diagnosis was confirmed by examining the sputum for *P westermani* ova.

The life cycle of the organism and its pathogenesis within the human host are well described (Figure 1).[2-6] A reservoir of this trematode exists in many wild animal hosts. The adult worms are 0.8 to 1.6 cm long, 0.4 to 0.8 cm wide, and 0.2 to 0.5 cm thick. Their ova are produced in the lung tissue of a mammalian host and are expelled by coughing. Miracidia are released from the ova in water. Snails serve as the initial intermediate hosts for the miracidia, which mature into cercariae. The cercariae, released in the water, then invade crabs, crayfish, and other crustacean hosts. Cercariae become encysted metacercariae that may be released from dead or injured crustaceans into the freshwater environment.

Human infection depends on the ingestion of uncooked or pickled crayfish, crabs, or other hosts that harbor the metacercariae. Metacercariae can be accidentally transferred to the mouth during the preparation of shellfish, even if properly cooked. Drinking water and eating vegetation from infested rivers or ponds have been implicated in causing infection. In humans, metacercariae hatch in the wall of the small intestine. The young flukes penetrate into the peritoneal cavity and migrate through the diaphragm and pleura into the lung. There they encyst as adult worms. The lung tissue surrounding encystment exhibits transient patchy densities. Cysts adjacent to a bronchus often rupture through the mucosa, discharging eggs into the sputum. These discharges cause coughing and hemoptysis. Heavy infestations may encyst in many other parts of the body.

Although most infections are asymptomatic, recurrent hemoptysis is the cardinal symptom of pulmonary paragonimiasis. Eosinophilia may be present. Chest radiographic findings generally mimic those of tuberculosis and are often nondiagnostic. The diagnosis is made by finding eggs in the sputum. Eggs swallowed from infected sputum may be found in stool. Western blot testing for *P westermani* is available from the Centers for Disease Control, Atlanta, Georgia. This test is considered more sensitive and specific than the complement fixation test (J. Fried and M. Wilson, MS, Centers for Disease Control, oral communication, October 1991). Serologic testing requires clinical correlation and thus is not a substitute for sputum confirmation. Serial sputum studies may be required to monitor patients receiving treatment for the parasite.

Regarding the cases described, certain observations deserve comment. Stool specimens of one patient did not contain ova and parasites. Ova may be found in some patients who presumably swallow their infested sputum. Testing the stool for ova and parasites has a low yield; neither is the sputum always positive. In those cases, a serologic test may be of help. A positive serologic test confirms exposure to the parasite but gives no information on where the infection resides. A positive sputum test, however, is completely specific for the presence of pulmonary paragonimiasis. Hemoptysis was the major complaint in each patient. We know of no studies that examine the incidence of paragonimiasis in patients with hemoptysis (in contrast to tuberculosis, for example). This question deserves further investigation.

The possibility that paragonimiasis is underdiagnosed in the central San Joaquin Valley is difficult to extrapolate. We know of no reliable figures as to the prevalence of paragonimiasis in the Southeast Asian countries of Cambodia, Laos, and Vietnam. In Thailand, the prevalence in humans has been as high as 3.6%.[7] China has reported prevalence estimates ranging from 15% to 45% in the southern provinces.[8] At present, *P westermani* is not known to be transmitted within the United States.

Praziquantel has superseded bithionol as the treatment of choice for pulmonary paragonimiasis because of its safety, high level of efficacy, and ease of use. It is noteworthy that all of these patients were in good health after physicians had proceeded with the appropriate treatment. When praziquantel was first released in the US during the 1980s, single-day therapy was considered appropriate for cure.[9] Because the disease persisted in some patients treated with single-day therapy, praziquantel, 25 mg per kg three times a day for two days, is now recommended.[10,11]

Summary

We describe four cases of pulmonary paragonimiasis in Southeast Asians who emigrated to the central San Joaquin Valley of California. Physicians should be alerted to the possibility of this disease in Asian patients with hemoptysis and pulmonary infiltrates. Paragonimiasis can masquerade as pulmonary tuberculosis, especially in patients from areas that are endemic for both the parasite and the tubercle bacillus. The ease and safety with which this infection can be treated, in contrast to tuberculosis, reiterates the importance of diagnosing this lung fluke when it is present.

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Commentary

Canada's Experiment With Health Insurance
Somewhere Over the Rainbow?

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These are stirring times for Canada. Politicians who have provided government-financed health insurance to all Canadians for more than 30 years are looking for politically acceptable ways to trim the health care system. There are even suggestions for a two-tiered, American-style system wherein people with more money get better medical care than the poor.

The outcome has implications not only for Canadians but for those Americans, including some in Congress and some groups of physicians, who believe that Canada's system holds the ideal solution to our own problem of rising health care costs and millions of citizens without health insurance.[1]

A case in point is Alberta, where the government is seeking ways to trim its budget. Albertans have enjoyed access to first-class medical care for years under Canada's publicly financed health care system, which is administered by the ten provinces with shared federal and provincial financing. But the costs have been rising at such a rate that three years ago Alberta's government was reported to have spent more than $3 billion, or almost a third of its entire budget, on health.

Faced with a spiraling provincial debt of more than $11 billion, the government set up a commission to figure out how to cut costs, with health care being the obvious target. The health future of Albertans is now the subject of a 370-page document aptly titled *The Rainbow Report: Our Vision for Health.*[2] The result of a two-year project by the Premier's Commission on the Future Health Care of Albertans, the report does not propose a departure from the present system of government involvement, but it strongly suggests measures that some believe depart from the original philosophy of Canadian government-sponsored care of equity and equal access to one that is more reminiscent of US policies.

By exercising regularly and eating properly, the report begins, Albertans can spend less time and money in hospitals and seeing their physicians. Before Canada had national health insurance, Albertans were self-reliant and uniquely able to cope with matters of their health. That national characteristic can be tapped again. The commission suggests that the government divert an additional 1%, or $30 million, of the provincial health plan's annual operating budget to programs of health promotion and the prevention of illness and injuries by 1995. It also recommends that secondary schools and universities become "role models for a healthy environment and practices" in the province.

Individual Budgets on 'Smart' Cards

To encourage an efficient use of the health system, the commission proposes that every subscriber to the Alberta Health Care Insurance Plan be given a specific annual health care budget based on his or her previous use of the system. Subscribers should also be issued "smart" cards containing a computer microchip on which their medical histories and personal health care allotments for the year would be electronically imprinted. When a subscriber visits a physician, an assistant would pop the card into a computer and read when the patient's last visit was, which tests were done, and what the physician prescribed, as well as how much money the patient has left in his or her government health care account. Those overspending their yearly allotment would be referred for counseling, while those using the system less than expected would get some kind of a reward. Such a system could decrease health care use by as much as 30% if smart cards were available, its proponents claim. Regarding extended health care services—home care and costs from chronic disabilities—the commission suggests that they be covered by direct government payments to patients to help reduce barriers and restrictions while "encouraging self-reliance and dignity." Such direct payments will require enabling legislation, however, which the commission suggests be put in place no later than 1993.

The commission thinks Alberta's health system is administratively unwieldy and that there is an urgent need to alter it. Currently, this involves more than 400 provincial boards and committees. The commission proposes to divide the province into nine autonomous administrative areas, with elected boards of trustees looking after the distribution of government funds and community care programs and facilities. In addition, the commission calls for the creation of a position of "Advocate for a Healthy Alberta." The advocate, with a $4.5 million annual budget, would conduct assessments of the health system and propose health care strategies.

Recommendations also include the establishment of a provincial ethics authority or center to provide grants to persons working on controversial medical issues such as organ transplantation, reproductive technologies, genetic medicine, and euthanasia. The commission thinks the government should initiate legislation to provide members of the public with the tools to make personal, financial, and legal arrangements before becoming incapacitated by major illness.

The report contains key recommendations for improving the well-being of care givers. They are intended to help ease the stress on the health care system's work force by encouraging management practices that recognize meritorious service, involvement in decisions regarding the provision of health services, programs directed toward resolving conflict, and incentives that create a safe working environment and

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good morale. Coupled with these measures is the need to monitor and evaluate health personnel requirements in the province to respond to the changing demands of patients and to relieve the stress on overworked, overextended health care professionals.

Emphasizing health promotion research, the commission asks that $33 million be allocated to the Alberta Heritage Foundation for Medical Research, dispersed over ten years, for studies in promoting healthy life-styles. In addition, it recommends an expanded mandate for the Alberta Research Council to evaluate the pros and cons of new health-related technologies, to develop strategies for distributing or rejecting technologies, and to assist, in conjunction with the private and public sector, in the successful transfer and marketing of Alberta-developed technologies.

Another provision concerns the environment. The government should expand the mandate of the Environment Council of Alberta, the commission says, to encourage greater research into environmental protection and the commercial production of "environmentally friendly" products.

Criticisms—'Dangerous Ideas, Glaring Omissions'

In the three volumes and 21 recommendations of the *Rainbow Report,* critics envision a hidden agenda to limit Albertans' access to health care. Despite public reassurances by commission chair Louis Hyndman that the report "strives to set the stage for the 21st century," critics charge it contains dangerous ideas and glaring omissions (K. Sherlock, "Brave New World of Medicine: Critics See Dangerous Ideas, Glaring Gaps in Rainbow Report," *Edmonton Journal,* February 24, 1990, p G1).

The report fails, they say, to offer concrete mechanisms for attacking one of the most important issues: the link between poverty and ill health. Similarly, mental health services are threatened because, like chronic diseases, psychiatric problems and their duration cannot be predicted, so it is ludicrous to penalize people for exceeding their health budget allotment. People should not be discouraged from visiting their physician, critics say, because early detection and treatment of an illness can prevent more serious and costly measures down the road.

What has generated the most heat from various sources is the recommendation that for the first time supplemental health insurance be routinely available to Albertans who wish to pay for and receive coverage over and above the basic services covered by the Alberta Health Care Insurance Plan. In addition, the commission proposes that alternative care givers such as native healers and herbalists be included in either the basic or supplemental plan. These recommendations, obviously aimed at saving the government money, mark a significant departure from the past policy of equity and equal access to medical care for all Canadians. Iglehart and Evans have pointed out that over the years Canada has refused to allow private insurance to be sold, except for incidental items not covered by the provincial plans, and that this reluctance arises from a deep-rooted suspicion of class-based systems.[3,4] The suggestion seems also totally out of character if one considers that Alberta is not just any province. With oil resources, rich agricultural and timber industries, tourism, and more than 50,000 people working in some area of health care, it is considered one of the richest in Canada (B. Hutchinson, "The Hyndman Manoeuvre: The Rainbow Report Looks to Save a Pot of Gold with a Streamlined Health Care System," *Alberta Report,* February 26, 1990, p 42).

Physicians Fear Risk of Two-Tiered System

In press statements, Ronald Gregg, MD, past president of the Alberta Medical Association, and Richard Plain of the Alberta Consumer Association have both praised but also criticized the report (K. Sherlock, *Edmonton Journal,* February 24, 1990, p G1). They said it opens the risk of a two-tiered system because it leaves the definition of basic services up to the government of the day, and the government has a record of trying to cut coverage for some services to save money. Alberta physicians are worried about cost-conscious governments deciding what is necessary. Instead, Gregg and others think society as a whole—not physicians or government alone—must, after complex calculations, define which services are appropriate for which types of patients and thus eligible for public financing. As costs continue to rise, physicians agree that new medical procedures will have to be examined objectively. The commission prudently did not define "basic" services; it has left the job of doing so to the politicians.

The Canada Health Act does not define "basic" or "medically required" health care, and this results in differences in services between provinces. For example, some provincial health plans now cover in vitro fertilization, but this procedure is not covered in Alberta. Such gaps in coverage have led to what the Alberta Medical Association describes as at least four tiers of care now available to Albertans. They include the Alberta Health Care Insurance Plan as it exists; those with supplemental coverage, such as Blue Cross, often enjoyed by labor union members; privately run clinics providing services such as eye and cosmetic surgery; and the United States—where wealthy Canadians or those who have saved their money for such purposes can receive treatment either not available in Alberta or Canada or for which there is an undesirable waiting time. Basic health services, according to the association, must be of high quality and ensure comprehensiveness, portability, universality, accessibility, and public administration. For services not defined as basic, Albertans must have the right to purchase coinsurance.

Although the Alberta Medical Association agrees in principle with many of the recommendations of the *Rainbow Report,* it has criticized the report for its "middle-class, if not an upper-middle-class, bias of what the future may be."[5] The report, the Association notes, makes only a passing reference to the spectre of poverty in the midst of above-average incomes, while "the salient reality is that people's health remains directly related to their socioeconomic status." A better approach would be for the health care system to evolve more comprehensive strategies to address the needs of different groups of society on a priority basis.

In supporting health promotion as a worthwhile goal, the association's analysis raises doubts that those Albertans who live at or near the poverty line can be expected to pursue a healthy life-style. Health promotion has its biggest payoff with children, the association states, and health goals specific to children and adolescents, such as improving diet and fitness and reducing smoking and teen pregnancies, should be considered. It recommends a greater emphasis on reducing workplace injuries and automobile accidents while cautioning that health promotion is not a financial panacea. "The financial impact of any positive life-style changes is

unlikely to be forthcoming for at least two decades (much longer than the tenure of most governments)."[5] The association also supports the intent of the recommendation on smart cards but has questioned their practicality and cost-effectiveness on grounds that they may become "cards of regulation" rather than cards of information. Another association concern is the recommendation for rewarding those who use the health care system considerably less than the norm. Actually, it will tend to reward those with upper-middle-class and upper-class life-styles and penalize those from the lower socioeconomic groups who suffer from poor health, including many accident victims who often require prolonged, expensive medical care through no fault of their own.

Because of the reaction to the commission's report, which has ranged from praise to outright indignation, Premier Donald Getty has asked an interdepartmental committee of the Ministry of Health to study the recommendations and develop a policy statement for their implementation. A ministry spokesperson said flatly that the government has no intention of moving toward a two-tiered system. In fact, four years ago, Alberta tried legislation that would have allowed private insurance companies to compete with the Alberta Health Care Insurance Plan. A public outcry compelled Mr Getty to withdraw the legislation. In a similar move, the province removed insurance coverage of several procedures, including tubal ligations, cosmetic plastic surgery, circumcision, and contraceptive counseling. After public complaints, coverage of some of the services was reinstated. It should be noted that Alberta is still the only province to consider a two-tiered approach as part of the solution. Recent inquiries in Ontario, Quebec, Nova Scotia, and New Brunswick indicate that these provinces have been thinking of ways to cut costs but have not broached the subject (C. McLaren, "Alberta: The Spectre of Two-Tier Medicare," *The Globe and Mail,* March 17, 1990, p D1).

Government insurance was introduced to Canada in four phases. First came hospital construction in 1948, followed by hospital insurance in 1958 and health personnel development in 1965. Finally, medical care insurance was started in 1968 to cover physicians' costs. In providing universal coverage, Canadians were motivated mainly by human concerns rather than economic objectives.[6] Their purpose was to remove barriers to health care. They decided that coverage had to be comprehensive, meaning it would pay for all medically needed services rendered by physicians or hospitals without limit. They determined that benefits would be portable when people moved from one province to another and that health insurance had to be operated on a nonprofit basis by public agencies accountable to the people.

Reduced Federal Cash Transfers Hurt Provinces

The system, which initially promised so much, has come under hard times, for many reasons. Canadians are aging. Their economy is growing at a slower pace. Hospitals within various regions are duplicating services, and provincial health care plans' payments to physicians are rising, with health services now gobbling a third of every province's budget. For a time in the late 1970s, Canada seemed to be succeeding in slowing the rise of health care costs through various measures. These involved closing surplus hospital beds, eliminating unnecessary services, and establishing a system of prospective payment for hospitals and negotiated fees for physicians. Even these measures are now deemed insufficient. Like Alberta, the federal government in Ottawa has stepped up its policies. In an attempt to reduce Canada's federal deficit, Prime Minister Mulroney's government has twice now, in 1986 and 1989, reduced the contribution of federal government funds to provincial plans. This is done by a new formula based on the growth rate of a three-year running average of the gross national product, minus three percentage points. Canada's gross national product, however, has been declining for three years in a row, and as Iglehart recently predicted, this decline is having a cumulative effect on provincial budgets.[3]

Specifically, federal money transfers from Ottawa to the provincial health insurance plans declined from 44.6% in 1979 and 1980 to 36.7% in 1989 and 1990 and are likely to continue to fall as a result of a new policy initiated by the federal finance minister as part of the 1990 federal budget. Under special legislation (Bill C-69), the per capita federal transfer payments to the provincial health insurance plans were frozen at the 1989-1990 level for two years. In the most recent, February 26, 1991, federal budget, the finance minister announced that this freeze would be extended for another three years. Because the original formula provides for both a tax transfer and a cash transfer, the freeze in total per capita transfers means that federal cash payments to the provinces are in fact being reduced, according to Bill Tholl, director of Health Policy and Economics of the Canadian Medical Association. "Federal cash contributions for some provinces are expected to drop to zero as early as 1994-1995," Tholl adds, "and in the absence of corrective legislation, this means that the national health insurance principles set out in the Canada Health Act will become unenforceable" (written communication, April 1991).

Tholl predicts that reductions in federal cash transfers can be expected to have a differential effect across the provinces depending on any number of factors. Chief among these is the "fiscal capacity" of a province. Poorer provinces such as Newfoundland with limited ability to generate additional tax revenue will have difficulty making up for the shortfall and have already announced major cuts in health programs. The richer Canadian provinces, such as Alberta, with a fiscal capacity 25% to 30% higher than that of any other province, are thought to have considerable fiscal flexibility and untapped potential to raise additional tax revenues necessary to offset the federal reductions. Alberta's $3.2 billion provincial health budget was scheduled for an increase of only 3% in 1990; public pressure eventually forced an increase of 4.1%, which is still below the projected level of inflation. The recent cuts in federal transfer payments have only added to the difficulty, which is being offset by an 8% increase in the provincial health care budget for 1991.

Problems with the Canadian system are documented in almost daily news accounts both in Canada and the United States. In Montreal, for instance, where provincial authorities had set a temporary cap on physician fees, many physicians decided to take two-week vacations every quarter, and hospitals shaved their budgets by holiday closings of wards and operating rooms. Patients backed up in the emergency departments, and one official of the Quebec Medical Society was quoted as saying, "We think the system is breaking down."

Some observers think these "horror" stories are exaggerated, and they cite the well-known tendency of the health care

sector to bleed profusely in the face of financial hits. Robert G. Evans, a Canadian health economist quoted in the *New York Times,* thinks the rhetoric of underfunding, shortages, and excessive waiting lists is now an important part of the process by which Canadian health care providers negotiate and gain their share of public resources—and their incomes (M. Freudenheim, "Debating the Canadian Health 'Model,' " *New York Times,* June 29, 1989, p C1). Another view maintains that because the government's control over payment is the principal means of regulating health care use, Canadian hospitals are forced to hold their costs below the available revenue to remain solvent. Faced with insufficient resources, hospitals resort to rationing services through queuing.[7(p15)] Patients are put on waiting lists for available hospital beds or for certain types of medical procedures or are literally lined up in hospital hallways awaiting care. In effect, Canadian providers decide who receives care and who does not by comparing the needs of each patient relative to all other patients. "The name of the game is to put your patient on as many lists as you can," one Canadian hospital official notes, "and whichever comes first, you admit your patient there."[8(p26)] Information collected by one Canadian public policy research organization suggests there are long waiting lists throughout most of Canada for laboratory tests and for high-cost surgical procedures such as hip replacements, cataract removal, and heart bypass procedure (J. Kosterlitz, "Taking Care of Canada," *National Journal,* July 15, 1989, p 1796). A related issue is the effect of cost containment on the diffusion of technologic innovation because of restraints on funding for capital acquisitions such as magnetic resonance imaging, lithotripsy, and organ transplantation.

Differences of opinion on such issues may reflect, of course, different views on the importance of state-of-the-art medicine in Canada and the US and may also reflect different medical practice philosophies. But figures, whether measuring the number of facilities offering various technologies or the number of persons that each facility serves, suggest that access to expensive technologies in Canada may be impeded.[9] An example cited is that in 1989 Canada had a total of four lithotripters in the entire country and at least one US hospital was receiving the overflow. In the first five months of that year, half of all lithotripsy patients at New York State's Buffalo General Medical Center were Canadians.[7(p16)]

While the Canadian system still has much to recommend it—no one is seriously thinking of abandoning it—developments in Alberta are throwing a spotlight on a key question now troubling policymakers in Canada, the US, Great Britain, France, and other developed countries: how much health care is enough, and which medical services will be considered essential and eligible for payment from government or private insurers in the future? Economic stagnation, coupled with world tensions and increasing military expenditures, has rendered the continued expansion of health care outlays unacceptable throughout the western nations. Austerity measures in health care will differ from one nation to another, depending on the political group in power and the degree of opposition in place. In fact, one political observer predicts a sharpening of ideologic cleavages in all policy areas, with a loss of public confidence in government emerging as the most important single issue in the future.[10] This is another reason why recent developments in Alberta are instructive.

It is clear thus far that Alberta's past attempts to ration health care, which is regarded as a basic right, have met with mixed success, and there is no reason to think that the most controversial recommendations of the *Rainbow Report,* if implemented, will fare any better. In each instance in the past, as in the example of cosmetic surgery, tubal ligations, and circumcision that were removed from insurance coverage, politicians had to acquiesce to public opposition by restoring coverage to avoid the destabilizing political repercussions. In fact, after a two-year review of the report, the government in January 1992 announced it had decided it will not implement several key recommendations it felt Albertans would perceive as undermining universality. These included the recommendations for smart cards, supplementary insurance for optional services, the appointment of a health care advocate for Alberta, and the reorganization of regional health authorities. To their credit, physicians' organizations have effectively reacted against the system and criticized it when the government's efforts to save money were in direct conflict with the interests of their patients. Canadian physicians seem able to mount an effective front against austerity efforts, and by their actions they also protect their incomes.

As for those Americans with a fascination for the Canadian approach, one thing is clear. It is not a panacea. Apart from better efficiency and fiscal control, as well as more equitable accessibility, Canada's system has left many issues unresolved. If the United States were to adopt a plan substantially the same as Canada's, there is no significant reason to expect that the US experience would be different in this respect. It is nevertheless a system whose continuing evolution is worth watching for those political lessons that are applicable to the US.

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Commentary

A Humanistic Library for Physicians by Physicians

JAMES K. GUDE, MD, *Santa Rosa, California*

Dr James Gude trained at Yale and Stanford and has been chair of the residency and library committees at the Community Hospital of Sonoma County for years. A former Fulbright scholar, he practices pulmonary and critical care medicine, teaches with passion and award-winning skill, savors the history of medicine, and lectures widely on subjects ranging from Greek, Roman, Arabic, and Chinese medicine to medical ethics and physical diagnosis. We present an annotated list of some of his favorite physician-authors and their work. We hope it inspires you and expands your horizons. Guenter Risse, MD, in his accompanying editorial, wishes you "Bon Appétit!" We hope you will also send us a list of your favorites; we will publish follow-ups from time to time.*

THE EDITORS

Every physician needs a humanistic library for support and discovery. There are two ways of defining humanism in medicine. The first is to define a humanistic physician as

> [O]ne who understands patients as people and considers their psychological and social features in his or her assessments and treatments, who is compassionate and ethically sensitive, and who communicates compassion and sensitivity warmly and effectively to patients.[1]

The second is to call forth the liberal arts traditions in medicine of philosophy, prose, and poetry centered on the human condition.[2]

William Carlos Williams (1883 to 1963) blended a compassionate caring for his patients with prose and poetry. He wrote,

> That is why as a writer I have never felt that medicine interfered with me but rather that it was my very food and drink, the very thing which made it possible for me to write. Was I not interested in man? I could touch it, smell it. It was myself, naked, just as it was, without a lie telling itself to me in its own terms.[3(p120)]

I share with you 13 books written by physicians in this liberal arts tradition of medicine.

Humanistic Writings of Physicians

François Rabelais (1494-1553) was a monk and then a physician who wrote with exaggerated humor and biting satire about the conflict between Scholasticism and Humanism. His *Pantagruel* (1532) and *Gargantua* (1534) are works ahead of their time.

John Locke (1632-1704) was a philosopher and physician who made bedside rounds with Thomas Sydenham, the English Hippocrates. Locke's *Second Treatise of Government* (1764) is a classic defense of the Western liberal constitutional state with the natural right of private property.

Oliver Goldsmith (1728-1774), a writer and physician, created a comedy in *She Stoops to Conquer* (1773) that presented the common man as foolish and erring but basically good.

John Keats (1795-1821) was among the greatest of English poets. He died of tuberculosis at age 25.

Johann Christoph Friedrich von Schiller (1759-1805) was a German dramatist and physician who was concerned about freedom. He wrote *The Robbers* (1780) when he was only 21 years old, and it bespeaks his wild, rebellious spirit. The Wallerstein trilogy (1799) further develops the dilemma of freedom in an historic figure, Wallerstein.

Sir William Osler (1849-1919) wrote,

> A liberal education may be had at a very slight cost of time and money. . . . Before going to sleep read for half an hour, and in the morning have a book open on your dressing table. You will be surprised how much can be accomplished in the course of a year.[4]

In 1906 Osler recommended ten books for a bedside library for medical students, and his *Aequanimitas* is one of my 1992 choices.

Sir Arthur Conan Doyle (1859-1930) fashioned Sherlock Holmes after his clinical teacher, Dr Bell, of Edinburgh Medical School. Holmesians abound in medicine.

Anton Pavlovich Chekhov (1860-1904) was a great Russian short story writer and dramatist. Dr Astrov in *Uncle Vania* presents a physician who only tolerated the present by believing that man could do far better.

W. Somerset Maugham (1874-1965) created in Philip of *Of Human Bondage* a physician who develops with loving humanity.

A. J. Cronin (1896-1981) presented an ethical physician in Andrew Manson, who sought the truth as he saw it despite the medical establishment's repressive actions.

William Carlos Williams (1883-1963) was a hard-working family physician and poet who raised Paterson, New Jersey, to an epic poem, "Paterson." *The Doctor Stories* reveal a clinician and writer who drew poetry and prose out of the lives of those patients whom he truly cared for. He is a model physician and humanist.

Walker Percy (1916-1990), a pathologist turned writer, wrote about the South with insights borrowed from medicine. Will Barrett in *The Second Coming* develops new understanding of his society through disease.

Lewis Thomas (1913-) has created essays, including the collection *The Medusa and the Snail*, in which he states, ". . . Montaigne simply turns his mind loose and writes whatever he feels like writing."[5(p147)] So does Dr Thomas, and it is delightful reading.

*See G. B. Risse, "Literature and Medicine," page 431.

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Editorials

Literature and Medicine

JAMES K. GUDE, MD,'s suggestions for a "humanistic library" elsewhere in this issue[1] focus on an increasingly popular relationship: the use of literature, some of it written by physicians, to open "new worlds of thought, insight, emotion, and experience," as one author recently expressed it.[2(pxi)] Indeed, Peschel's collection of critical essays, *Medicine and Literature,* closely examines medicine in literature, including the motivations of medical writers such as Rabelais, Chekhov, Williams, Schnitzler, and Selzer, who wrote eloquently about the experiences of doctoring in past and recent times. "Medicine and literature are united in an unremitting paradox: the need simultaneously to stand back from and yet to share in the struggle of human life," wrote Edmund Pellegrino, introducing the work.[2(pxvii)]

This is as it should be. Literature has traditionally been a part of the humanities, a field that embodies particular ways of thinking, judging, and articulating the sources and essences of our humanity. Far from being only the foundation for a number of scholarly disciplines, the humanities provide an operational approach to help all of us understand our lives. Moreover, there is a social scope to such endeavors, since through the use of language they allow us to share our emotions and reflections with others. For contemporary medical writers such as Michael Crichton, "the assimilation of important experiences almost obliges you to write about them. Writing is how you make the experience your own, how you explore what it means to you, how you come to possess it, and ultimately to release it."[3(px)] Relationships between medical narrative and knowledge as reflected in the clinical history are among the issues currently under study.

If the writing of literature can be a liberating and even a healing experience for authors, readers will likewise benefit. The literary experience is potentially a humanizing factor in any life, but especially so for members of the health profession, who must display greater empathy and compassion toward human illness and death. Physicians with an enhanced sensitivity to language might well be better equipped to understand the values, emotions, and sensitivities of their patients. As one author postulated, "the concrete and sensuous experience of language afforded by poetry possibly contributes to a greater awareness, for both the speaker and listener—writer and reader—of what is being said and felt in many an interchange of daily 'professional' life."[4(p148)]

In their pursuit to examine and question the presuppositions on which their professional and private lives are based, physician-authors in their works have returned to the world of human suffering, not only narrating their experiences but sharing with readers their emotions, reflections, and judgments. "We doctors are, by and large, a sentimental, humane lot. Moved by the suffering of our patients, we tend, when writing, to produce poems, essays, and stories that are sentimental and humane," admitted Richard Selzer.[5(p40)] Faced with a dying patient who received therapy despite vigorous refusals, Crichton confessed that the episode troubled him for the rest of his brief medical career and prompted him to quit practicing medicine.*

*The issue of the physician as a writer was admirably discussed in the 1970s in a series of dialogues organized by the Institute on Human Values in Medicine. The five meetings took place between May 1975 and July 1976.

As recent publications have pointed out, the relationship between medicine and literature is often explored in medical schools today. Literature in medicine, especially in medical education, has been part of the educational reform movement of the 1970s. Some authors, like Selzer, have even questioned current medical school admission policies, stressing the importance of intuition, compassion, and ingenuity, the "trinity of doctorhood."[6] The return of the humanities to the curriculum, in turn, has been the objective of prominent medical educators, notably Dr Edmund Pellegrino. As one recent report concluded, "language commands a central place in the practice and culture of physicians. Through the surrogate experiences of imaginative literature, the young physician can enlarge and supplement his or her store of experience."[7] For the spring quarter, the Department of the History of Health Sciences at the University of California, San Francisco, has scheduled an elective, "Poetry in Medicine," to be given by David H. Watts, MD. This course will examine the use of poetry to express human qualities and emotions that arise around issues of health and disease. Specific examples will be drawn from the world's poetry; their creative and political implications will be discussed. Among the course requirements will be the writing of several new poems.

For physicians searching to "tonify their souls," a scholarly journal, *Literature and Medicine,* offers ample nourishment. Under the editorship of Anne Hudson Jones since 1982, this yearly publication of the Johns Hopkins University Press has brought original contributions from physicians and fiction writers, arranged according to particular themes, such as the images of healers, the physician as writer, psychiatry and literature, as well as literature and bioethics. A general anthology of primary materials can be found in Ceccio's *Medicine in Literature.*[8] Equally useful is the second edition of Trautmann's (now Banks) *Literature and Medicine,* an annotated bibliography of literary works dealing with health-related subjects. This book is not only chronologically arranged and divided by topics but contains brief summaries of the cited works.[9] Finally, readers will enjoy two recent anthologies, one of them assembled by Cousins on physicians in literature.[10,11] Bon appétit!

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Cervical Cancer Control in Minority Women—More Needs to Be Done

THE ARTICLE by Becker and co-workers appearing elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE presents trends in cervical cancer incidence and mortality among Hispanics, Native Americans, and non-Hispanic whites in the state of New Mexico.[1] The availability of data for a long period of time and the high-quality surveillance systems in this state make the information provided in this report unique. While the article documents notable achievements in decreasing the incidence and mortality of cervical cancer among specific population groups, it also indicates the need for further cancer control activities.

When cervical cancer incidence patterns in New Mexico were compared for two periods (1970 to 1978 and 1980 to 1987), substantial declines (approximately a fourth to a third) were noted among all three population groups.[1] The incidence of invasive cervical cancer among both Hispanics and Native Americans continued to be high in comparison with non-Hispanic whites, however. Among the ethnic-racial groups in the United States, Native Americans in New Mexico had one of the highest incidence rates for invasive cervical cancer during the period 1977 through 1983 (J. Horm, MS, National Cancer Institute, written communication, May 1991). The incidence of in situ cervical cancer also decreased and became comparable among these three groups during the period of observation. Among Hispanics and Native Americans, age-specific incidence rates for both invasive and in situ cervical cancer were found to diverge considerably from age-specific rates among non-Hispanic whites in the later age groups.

Despite these documented decreases in cervical cancer incidence and mortality, disease patterns for cervical cancer during recent time periods indicate the need for continued efforts directed toward eliminating the disparities that continue to exist. In the publication *Healthy People 2000*,[2] the Public Health Service has developed objectives for a national initiative aimed at preventing deaths and reducing disease and disability during the coming decade. *Healthy People 2000* proposes the goal of a reduction in cervical cancer mortality from a national rate of 2.8 per 100,000 in 1987 to not more than 1.3 per 100,000 by the year 2000. In the context of this objective, continued public health intervention is necessary because cervical cancer mortality rates in New Mexico during 1983 through 1987 among non-Hispanic whites (1.8/100,000), Hispanics (3.9/100,000), and Native Americans (4.8/100,000) exceeded this goal.

Data from this report are specific to the state of New Mexico, but the general patterns of disease are consistent with previous reports noting an increased incidence and mortality of cervical cancer among both Hispanic and Native American women. Although Hispanics and Native Americans both include heterogeneous groups, consistency in cervical cancer patterns has been observed within these groups. Excess cervical cancer rates have been described among Hispanic populations residing in different geographic areas.[1,3] In addition, in a meta-analysis of cancer incidence patterns among Native Americans, we noted a generalized elevation in cervical cancer incidence.[4]

A constellation of risk factors for cervical cancer has been identified, including age at first coitus, number of sexual partners, non-white race, lower socioeconomic status, sexually transmitted viruses, cigarette smoking, oral contraceptive use, and selected dietary components. Several analytic studies have explored cervical cancer risk factors among Hispanics in various geographic areas, but the cause of their excessive susceptibility remains undetermined. Analytic studies of cervical cancer among Native Americans have not been completed.

Widespread cervical screening results in an earlier stage at diagnosis with reduced mortality.[5,6] A Papanicolaou screening test should be completed for all sexually active women at an interval of one to three years, or more frequently if recommended by a physician. Unfortunately, a sizable proportion of women do not receive a Papanicolaou screening test on a regular basis. At present, 75% of women in the general population report obtaining a Papanicolaou smear every one to three years.[2] Among Hispanic women, 66% report obtaining a Papanicolaou smear within this interval.[2] Papanicolaou screening practices among Native Americans are unknown. It is important to expand our understanding of preventive health practices among Hispanics, Native Americans, and other special populations in an effort to identify potential intervention strategies. The limited data currently available indicate that more comprehensive information on cancer screening practices among special population groups needs to be collected, analyzed, and applied in future interventions.

Given the unique cultural milieu of special populations, these groups are unlikely to be responsive to a cancer education campaign of health promotion messages targeted to the general population. Barriers to the use of cervical cancer screening services, whether they relate to cultural or health system obstacles, need to be overcome. Community representatives and health professionals need to work cooperatively to develop culturally relevant and sensitive cancer control messages. Cancer education materials should communicate an understandable message and promote the adoption of personal preventive health practices. Efforts to develop culturally appropriate cancer education materials for special populations are components of community-based research studies currently under way in several communities across the United States.

Health care professionals in the primary care setting should recognize the special responsibility to promote and to provide cancer screening services, including for cervical cancer. It is also necessary to ensure the prompt follow-up of women with unusual cytologic results.

Cytologic screening and providing risk reduction materials represent cost-effective means of reducing both the economic and the social effects of cervical cancer in special population groups. It is hoped that primary care providers and public health professionals can assist in promoting the use of cervical cancer screening services. Further reductions in cervical cancer incidence and mortality, particularly among women of special population groups, remain as an important public health challenge.

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Pheo or Not a Pheo, That Is the Question

THE ADRENAL GLANDS have fascinated physicians over the centuries. The first anatomist to give a detailed description of the human adrenal glands was Eustachius in the 16th century, but his observations were unpublished for some time.[1] Surprisingly, the adrenal glands were described as hollow by Bartholin in the 17th century. This concept was corrected in the 19th century when it was clearly recognized that the adrenal glands were solid structures and that there were two portions of the adrenal gland, the cortex and the medulla. The advent of microscopy and histochemistry provided definitive proof that the medulla was a distinct part of the adrenal gland. The chromaffin reaction, a brownish deposit in the adrenal medulla after the fixation of catecholamines in chromic acid, or dichromate salts, was described in the middle of the 19th century. Epinephrine was among the earliest hormones discovered and was isolated in crystalline form and the chemical structure elucidated in 1897. It was synthesized in 1904 and later was shown to be present in increased amounts in patients with pheochromocytoma.

In 1886 Fränkel described the case of a young woman with the symptoms of a pheochromocytoma in whom, at autopsy, bilateral adrenal tumors were found. In 1922 Labbé reported a case and was the first to attribute the symptoms to the adrenal tumors. The next year, Professor Villard of Lyon operated on a patient who died in shock. In 1926 C. H. Mayo at the Mayo Clinic and G. Roux in Switzerland successfully removed adrenal tumors and dramatically reversed hypertensive episodes.

Over the midportion of the 20th century, the identification of norepinephrine, dopamine, other precursors, and metabolites led to rapid advances in the biochemical diagnosis of pheochromocytoma. Precision in the measurement of these compounds was further refined by high-pressure liquid chromatography and radioisotopic labeling techniques, which have substantially contributed to the preoperative diagnosis and follow-up in patients with catecholamine-producing tumors. The development of scanning techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), as well as radioisotopic (iodine 131) labeling of *m*-iodobenzylguanidine (MIBG), has greatly contributed to the preoperative localization of tumors. The recognition of the significance of abnormal DNA ploidy, that is, that this is associated with the potential for malignancy, has considerably improved patient care and follow-up.

Pheochromocytoma is a rare tumor that can occur at any age, but the peak incidence is in the fourth through the sixth decades. Among the general population of Olmsted County, Minnesota, the incidence of pheochromocytoma is 9.5 per million population per year, in the Netherlands 0.4, Denmark 1.9, and Sweden 2.1. These rates vary, largely related to the acquisition of the material, both clinically and at autopsy. The incidence of pheochromocytoma among hypertensive persons has decreased greatly, largely because essential hypertension has been diagnosed in more people in recent years as the blood pressure limit for normal has been lowered. For example, from 1973 to 1975, the annual incidence of pheochromocytoma at the Mayo Clinic was estimated to be 0.4 per 1,000 hypertensive persons with diastolic pressures of 95 mm of mercury or more. Pheochromocytoma continues to be a diagnostic challenge as a substantial proportion of cases of pheochromocytoma found at autopsy are still undiagnosed clinically.

Pheochromocytoma may be part of a polyglandular endocrine derangement or may be associated with other neuroectodermal disorders. There is an increased incidence in families, particularly when the index case is a child with pheochromocytoma and also when pheochromocytoma is present in both adrenal glands. Autosomal dominant inheritance is seen in persons with multiple endocrine neoplasia (MEN) type II, in association with pancreatic islet cell tumors, and in neuroectodermal disorders (such as neurofibromatosis and von Hippel-Lindau disease). Families with multiple adrenal and extra-adrenal pheochromocytomas unassociated with other tumors or syndromes also have been reported. The Carney multiple neoplasia triad of extra-adrenal paragangliomas, gastric leiomyosarcomas, and pulmonary chondromas is a rare but interesting triad of rare tumors that is not familial. Almost all of the reported Carney cases have been in young women, and the finding of any two components of this triad should raise serious consideration of this syndrome.[2]

Pheochromocytoma is not caused by a single genetic defect. The genetic locus for this tumor has been attributed to chromosome 10 for MEN II, chromosome 17q for neurofibromatosis type I, chromosome 22 for neurofibromatosis type II, and chromosome 3p for von Hippel-Lindau disease. In nonfamilial cases, several genetic locations have been attributed.

Pheochromocytoma arises from chromaffin cells that are located in the adrenal medulla, but also in paragangliomas, which may be located anywhere from the base of the brain—such as the glomus jugulare—to the testicle, including the mediastinum and inside the heart arising from the interatrial cardiac septum and within the myocardium itself. Most (90%) pheochromocytomas arise in the adrenal medulla, and most of the extra-adrenal tumors also occur in the abdomen. This information is helpful when planning imaging studies.

Malignancy is more frequent in extra-adrenal tumors and when tumors arise in young persons. The incidence ranges from 3% to 14%. Nuclear DNA-ploidy studies by flow cytometry have shown that patients with a normal DNA histogram follow a benign course, whereas 30% to 40% of the remainder have or develop evidence of malignant disease in follow-up studies.[3]

In the article on pheochromocytoma elsewhere in this issue of the journal,[4] Philip Cryer, MD, describes the physiology of the sympathochromaffin system and notes the potential of the cells to produce a vast array of peptides and other compounds.[2] The biologic action of these compounds in contributing to the symptoms of pheochromocytoma, in addition to the symptoms attributable to catecholamines, is unclear. While paroxysms of hypertension are by far the most com-

ABBREVIATIONS USED IN TEXT

CT = computed tomography
MEN = multiple endocrine neoplasia
MIBG = *m*-iodobenzylguanidine
MRI = magnetic resonance imaging
VMA = vanillylmandelic acid

mon clinical symptom, occasionally pheochromocytomas may be asymptomatic and are found serendipitously. In other rare instances, hypotension and polyuria are prominent in patients whose tumors produce predominantly epinephrine or dopamine. On occasion, the erratic blood pressures are clearly shown on ambulatory blood pressure monitoring where both symptomatic and asymptomatic paroxysms of hypertension and orthostatic hypotension can be demonstrated. While not diagnostic, this pattern suggests the diagnosis.[5]

Although the family history, the symptoms, and the findings of a physical examination may give clues to the presence of one of the heritable syndromes and to sporadic pheochromocytoma, the diagnosis must be made on the biochemical determination of the excess production of catecholamines and metabolites. In rare instances, totally asymptomatic and biochemically negative tumors may be found, but almost always when these patients are operated on, manipulation of these tumors causes cardiovascular crises. Computed tomographically guided needle biopsies of pheochromocytoma in the absence of α- and β-adrenergic blockade—as in the preparation for any surgical procedure in these patients—can be hazardous.

The question of which test or tests to use in screening is not an easy one to answer.[6,7] Any single test chosen may be negative on occasion, but most are positive in all patients. Given an excellent biochemical technique for measuring the particular substance, the decision then comes down to practice style. When a well-measured 24-hour urine specimen can be obtained, the measurement of metanephrine excretion is the least invasive and most economic screening test. A measurement of vanillylmandelic acid (VMA) levels is almost as good. In any case, an abnormal screening test result should be confirmed by all three tests: fractionated free catecholamines, metanephrines, and VMA. A well-timed urine collection of less than 24 hours' duration, related to creatinine concentration, can also be used; it is thought that an overnight collection is best because of the reduced sympathetic activity during sleep, and thus an autonomous hypersecretion of catecholamines can be measured more readily. Plasma catecholamine levels are useful in confirming the diagnosis when the specimen is obtained under carefully controlled circumstances, as described in Cryer's article.[2] There can be great biologic variation and marked changes in plasma catecholamine levels under many physiologic and nonpheochromocytoma situations. It is important to reiterate that the specimens for measuring plasma catecholamine levels are best drawn with an indwelling catheter in a basal state. When doing biochemical tests, it is important to recognize the physiologic and other circumstances that can interfere with the interpretation of the test. In addition, specific interference—such as the presence of methylglucamine, a component of many iodine-containing contrast mediums—will falsely lower metanephrine levels for as long as 72 hours after its use parenterally; methenamine mandelate consumes catecholamines within the urinary bladder; clofibrate can reduce the concentration of VMA in the urine. Labetalol hydrochloride, a drug commonly used to manage pheochromocytoma, can interfere with *all* of the biochemical determinations.[4] It is rarely necessary to use pharmacologic tests, but, if desired, provocative tests using histamine, glucagon, and metoclopramide and a suppressive test with clonidine could be considered.

After the diagnosis has been considered clinically and confirmed biochemically, preoperative localization should be attempted because of the many locations in which a functioning pheochromocytoma may be found. Magnetic resonance imaging will likely become the preferred technique as it becomes more universally available. It identifies the adrenal lesions as well as CT but is better for extra-adrenal tumors. Magnetic resonance imaging does not require the administration of any glucagon or contrast media, which can provoke a catecholamine crisis, unless the patient is protected with α- and β-adrenergic blockade. Scintigraphy has not proved to be as useful as other imaging procedures in the initial evaluation of patients, although the entire body can be imaged. There is a 10% to 20% false-negative rate. Labetalol use and that of many other compounds interfere with the uptake of the isotope by catecholamine-containing cells.[8] At the Mayo Clinic, with sporadic cases of pheochromocytoma, when CT of the adrenal areas, the rest of the abdomen, and the pelvis is negative, [^{131}I]MIBG scintigraphy directs the next location to image with MRI. Scintigraphy using [^{131}I]MIBG has an important place in the evaluation of familial cases in patients in whom the presence of metastases, multiple tumors, or extra-adrenal tumors or malignancy is being considered. For example, we recently saw a patient in whom [^{131}I]MIBG scintigraphy located a metastasis behind the left clavicle following a normal CT examination of the chest and abdomen. This was clearly shown on MRI.

Preparing a patient for the surgical excision of a pheochromocytoma is as critical as the operation itself. The effects of catecholamine storms on the body can be prevented by appropriate adrenergic receptor blockade. α-Blockade is initiated until the patient is normotensive with slight orthostatic hypotension. Oral fluid and sodium loading restores the intravascular volume. β-Blockers are added for three days before the operation in almost all patients unless there is cardiomyopathy present. α-β-Blockers such as labetalol can be successfully used in many patients, but individual patients may not respond as well as to α- and β-blocking drugs administered separately in full doses. In a patient who does not respond as well as expected to adrenoreceptor blockade, consideration should be given to using converting enzyme inhibitors because renin levels are often elevated in these patients; sometimes this is due to inadequate volume repletion at the same time as the adrenoreceptor blockade is being initiated. Calcium channel blockers or the rate-limiting enzyme inhibitor, metyrosine, can be considered also. During the operation, blood pressure and arrhythmia monitoring and control are imperative, and the use of intravenous sodium nitroprusside is routine. Other parenteral drugs that can be used include labetalol, nicardipine hydrochloride, nitroglycerin, phentolamine mesylate, adenosine, and esmolol hydrochloride. As indicated by Cryer, a postoperative urine collection for catecholamine and metabolite analyses a week or longer after the operation is an essential part of the management to be certain that all of the abnormalities have resolved and that

there is no residual functioning tumor. DNA ploidy of the tumors should be measured and assigned the highest grade of several specimens. When DNA is normal, follow-up can be limited to repeating biochemical tests if symptoms recur. For those with abnormal ploidy, annual biochemical studies, such as 24-hour urine collections by mail, should be carried out indefinitely because the malignancy rate may be as high as 30% to 40%.

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Congenital Heart Disease—The First Test

IN THIS ISSUE of the journal, one of the deans of pediatric cardiology tells of the history and physical examination clues in diagnosing congenital heart disease.[1] Arthur J. Moss, MD, Emeritus Professor and former chair of the Department of Pediatrics at the UCLA School of Medicine, has long championed the clinical diagnosis of heart disease in children. In this high-tech world, that approach may seem out of favor. Now, with cost containment being an ever-increasing issue, it is well that attention be paid to the diagnostic pearls of an acknowledged pioneer and expert in diagnosing children's heart defects.

The history and physical examination should be regarded as the number one noninvasive test to be applied in making cardiac diagnoses. Yet, it is not uncommon for providers of primary childhood health care to do an echocardiogram when the question of heart disease arises. Despite its accuracy when expertly done, this is an expensive test. In addition, the echocardiogram is often done in a community hospital setting by a technician who does the test on one or two children and a few infants each month. The recorded tape may be sent to a center where the reading pediatric echocardiographer does not see the needed views and ends up reporting that "clinical correlation is necessary." In contrast, applying the clues described by Moss may obviate the need for further testing. At the very least, these historical and physical clues make intelligent referral possible and save thousands of dollars.

As noted by Moss, the age at which a cardiac diagnosis is suspected influences diagnostic possibilities. In the newborn, most often the discovery of cyanosis, respiratory difficulty, or a heart murmur leads to the consideration of a heart disorder. If all three coexist, the likelihood of heart disease is great. In this setting the respiratory distress equates to heart failure. In the first week of life, heart failure is most often caused by a transposition of the great arteries, the coarctation syndrome, or a hypoplastic left ventricle. Persistent truncus arteriosus may be added to the list. All of these defects may have associated cyanosis or at least decreased arterial oxygen saturation. All are treatable by surgical intervention in early life. Thus, respiratory distress in the first days of life, when thought to be due to a heart defect, requires pediatric cardiac consultation, not an echocardiogram.

On the other hand, neither cyanosis nor the presence of a heart murmur necessarily means that a heart defect is present. The need to distinguish central from peripheral cyanosis in a newborn infant is well discussed by Moss. As noted, cyanotic lips are generally a manifestation of peripheral cyanosis. The same is true for distal extremity cyanosis. On rare occasions, peripheral cyanosis of the extremities may extend to the arms and thighs. The condition may last for several months and is entirely benign. Some think this condition is caused by vasomotor instability. Regardless, simple in-hospital or office observation of the buccal mucosa while the baby cries usually distinguishes whether the cyanosis is central. The mucosa becomes cyanotic only with central cyanosis.

The discovery of a heart murmur in a newborn should not be a cause for alarm. A rule of further help to practitioners is to "judge all heart murmurs in the company they keep." A newborn with a systolic murmur who has none of the historical clues listed by Moss, is well formed, has no associated physical findings, and feeds well should be regarded as having a normal murmur. The baby in question needs only careful cardiac examinations in the course of a well-baby-care program. An echocardiogram is not necessary. An electrocardiogram and chest x-ray film are also of little help. More than half of all normal babies will have a heart murmur whereas fewer than 1 in 100 will have a heart defect. Pediatric cardiac consultation likewise may be postponed, for many of these murmurs will resolve.

The pitfalls of mistaking a murmur as normal when in fact a heart disorder is present are minimal in an overtly well infant, provided pulmonary hypertension or a hypertrophic cardiomyopathy is not present. The former can lead to hypertensive pulmonary vascular disease, an inoperable state, and the latter to sudden death, although usually not until school age. Pulmonary hypertension is marked by a loud second component of the second heart sound (loud P_2). A loud P_2 is normal in a newborn, but not after the first few weeks. The presence of a left parasternal impulse (right ventricular heave) in an infant with a loud P_2 should alert the practitioner to the possibility of pulmonary hypertension. Cardiac consultation would then be indicated. Should a mild or moderate heart defect without pulmonary hypertension be missed in early life, it will generally become clear on subsequent examinations and not be a cause of grief.

In a similar vein, when a child is discovered to have a murmur, the same rule of judging the murmur's sound in the context of associated historical and physical findings, particularly a normal growth pattern, needs to be applied. Again, the vast majority will be found to be normal.[2] An especially valuable point to remember is that normal murmurs tend to be short; that is, they end well before the second heart sound. A sound-free "space" may be heard just before the second sound, which is in itself normally split and not loud. Of course, this does not apply to the venous hum so well described by Moss. I would like to advocate that murmurs not associated with heart disease be labeled "normal" and cou-

pled with a second diagnosis: "no heart disease." It should then be clear to parents, other health care workers, and school authorities that the child does not have a problem and should be allowed full participation in the activities of childhood, including all types of sports. The term "functional murmur" should be reserved for pathologic conditions that cause heart murmurs but have normal cardiac anatomy. Typically, anemia and thyroid disease are associated with functional heart murmurs.

Another normal murmur, not elaborated on by Moss in this issue, is fairly common in older children. About 5% of normal teens will have benign carotid bruits. These harsh ejection systolic murmurs are heard best in the neck. Like other normal murmurs, no associated findings are detectable in a healthy teenager.

Chest pain is seldom a signal for alarm. In childhood, it is seldom due to heart disease in the absence of the provided clues. An exception may be mitral valve prolapse, which is found in about 1% of boys and about 5% of girls. Mitral valve prolapse is characterized by a mitral valve late systolic click or murmur. These sounds are heard close to the second sound. Thus, they will be preceded by a sound-free space heard after the first heart sound. Because echocardiographic findings have been confused in the past, pediatric cardiac consultation is warranted before making the diagnosis of mitral valve prolapse.

The many syndromes listed in Moss's article and certain situations noted here call for pediatric cardiac consultation. This is a relatively small number of patients, however, when compared with all those who might be referred for murmur evaluation. Accordingly, a scheme for pediatric cardiology referral is in order. Thriving asymptomatic infants and toddlers who are free of signs of pulmonary hypertension need only usual health care, although a cardiac evaluation should be done at each follow-up visit. If parental anxiety cannot be allayed, consultation might be in order. In most instances, a careful explanation about the nature of the murmur will obviate the need for referral. At school age, if hypertrophic cardiomyopathy cannot be ruled out, referral is indicated. For the latter purpose, the historical clues and recommendations noted by Moss are important factors. In a few instances, it may be difficult to differentiate an athlete's heart from hypertrophic cardiomyopathy. This requires pediatric cardiology assessment.

The goal of cardiac evaluation in children is to provide them with a sense of well-being and the opportunity to participate in those activities of youth that they desire. Only a relatively few children who have severe defects will need to be kept out of strenuous activities. Others with moderate to severe defects are best kept out of strenuous competitive sports.[3] The application of Moss's principles as the first test will initiate the decision making for this important purpose.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

The Suffering of Dying Doctors

To the Editor: In the January issue of the journal, Dr Bortz reported that a group of physicians in Palo Alto, California, follow good health care practices.[1]

These findings play an interesting counterpoint to informal observations I have been making during the 22 years since my internship, when I first noticed that physicians seemed to be notably underrepresented in the ranks of the slowly and painfully dying.

In the intervening years, I have made it a practice to ask health care providers of all disciplines if they have known physicians to die slowly and painfully, using large numbers of interventions such as surgery, chemotherapy, or radiation in the meantime. The responses have uniformly been in the negative.

Having tested "solid hunches" many times, I am painfully aware of their frailty against hard data, but it does occur to me that a systematic survey of physicians concerning their plans to facilitate their own death in the event of the early findings of chronic serious illness may be in order. If the findings confirmed my hypothesis that physicians commonly implement such plans and avoid the agony that we often facilitate for others, we would be in a position to speak somewhat more frankly to the nonmedical public concerning our views on chronic illness, suffering, and death.

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Magnetic Resonance Imaging for Marrow-Infiltrating Neoplasms

To the Editor: A recent report in the journal, "The Numb Chin in Metastatic Cancer,"[1] is an important contribution documenting the great sensitivity of magnetic resonance imaging (MRI) for marrow-infiltrating neoplasms. The article, however, contains an error. Also, the discussion of MRI technique, and particularly the use of gadolinium-diethylenetriamine penta-acetic acid (DTPA), is incorrect.

Figure 1 was described as a T2-weighted image after gadolinium-DTPA administration; the low signal intensity of the cerebrospinal fluid and the very high intensity of fat on that image, however, indicate that it is not T2-weighted but, rather, a T1-weighted (short TR, short TE) image. T2-weighted images are rarely indicated or used after gadolinium enhancement, particularly for assessing the bone marrow. T2-weighted images are time consuming and do not show bone marrow tumors well. Contrast enhancement does not produce diagnostically useful changes on T2-weighted images of bone marrow disease.

It is important to note that for detecting marrow infiltration, unenhanced T1-weighted images always should be obtained first.[2] They may be all that is required. Gadolinium enhancement may obscure tumor in the bone marrow because enhancing malignant lesions often become isointense (of equal brightness) to adjacent normal marrow. Enhancement may be helpful to confirm that an abnormality is more likely malignant than benign, but it is certainly not the preferred or initial approach. In Figure 1 of the article by Drs Harris and Baringer, the marrow-infiltrating process depicted is most notable for its relative *lack* of enhancement. This is usually seen with metastases that are predominantly osteoblastic.

For marrow-based or spinal malignant tumors, we recommend a combination of short TR-short TE (T1-weighted spin-echo) and STIR (short TI inversion recovery) images.[2,3] Gadolinium-enhanced T1-weighted images are selectively indicated, such as when symptoms suggest possible involvement of the spinal cord or intradural or epidural spaces, and then only after noncontrast T1-weighted images have been obtained.

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* * *

Drs Harris and Baringer Respond

To the Editor: Drs Porter, Smith, and Stimac are correct in identifying the image reproduced in "The Numb Chin in Metastatic Cancer" as being a T1-weighted gadolinium-enhanced magnetic resonance imaging scan. We designated the photograph as a T2-weighted image and apologize for the error.

Because this patient was evaluated for a cranial mononeuropathy, gadolinium was selectively used to assess for trigeminal nerve enhancement along the nerve's entire course. The presence of a bone marrow lesion was not known at the time the scan was done. We did not mean to imply that gadolinium was required in the image reproduced and agree with the respondents' comments regarding the use of T1-weighted scans and the administration of gadolinium.

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The Descendancy of the Educated Class

To the Editor: The debate on the delivery of our nation's health care rages on the network news nightly and on the political stage daily. Physicians are denigrated with the same zeal that our predecessors were apotheosized. Amid this cacophony, it becomes ever more difficult to attend to our societal and personal sworn duty of caring for the ill and tending to the infirm. The routine intrusion of the nonphysician on our educated decisions and the implications of dishonesty regarding our provision of care by the bureaucracy erodes our professional confidence and effaces the ancient numinosity of the physician-patient relationship.

No physician wishes to see anyone suffer the lack of health care. Since the dawn of western civilization we have accepted the responsibility of caring for our fellows without regard to their station in society. And because of this oath, across many borders and centuries of time, the evolution of consistently better health care has resulted. The commitment of multitudes of professionals to their art and science has made the citizenry of the developed countries the recipients of health care that is the apogee of achievement in this area of human endeavor.

This laudable state was not achieved by government, business, unions, insurance concerns, or securities exchanges. It was the result of focused attention and perspiration coupled with the educated frontal lobes of the human brain. If historical perspective is germane, then we as a culture and a nation seem to be at a juncture faced by other great civilizations recorded in recent and remote human history. Always, as cultures flowered and matured, the educated were afforded privilege and revered for their knowledge and skill—rewarded, it would seem, for the finesse of forebrain function. Recently, a change in the public's perception has occurred. Skill, knowledge, and the elegant use of the educated, integrated cerebrum are no longer valued. This change in view is not limited to medicine but has embraced engineering, education, business, politics, and law. The educated professional in America is jealously and circumspectly regarded as enjoying privilege that is unearned.

We do not know the reason for this change in attitude on the part of our populace, but it is not one shared by the cultures in ascendancy. Patently, changes of this magnitude evolve over time, and their desultory effects on us individually may be limited. But make no mistake, we are alive to witness the descendancy of the educated class in America and perhaps the developed world. Whether this process will be interrupted or can be interrupted is unknown, but of the result we can be sure. The decline of the professional class precedes the decay of the culture.

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Lessons From the Practice

Good Night, Joyce

GLENN FLORES, MD, *New York, New York*

As I step off the elevator, colorful cartoon characters, animals, and balloons greet me as I enter the Children's Cancer Ward. I am always momentarily confused by these vivid murals. The multitude of smiling figures positioned haphazardly on an empty background seem at first glance to be hovering and darting menacingly, but when I look again, the figures greet me cheerfully and placidly.

The hallways here are airy and well-lighted, even now in the early evening. I like the Children's Cancer Ward. Most of my physician colleagues detest it. They say it is too depressing. They assert that it is too overwhelming, that they would soon "burn out" if they worked here every day. But I look forward to working on this ward because to be with children with cancer is to be immersed in the realities of life.

A gaunt, bald 8-year-old child in a flowing, oversized white hospital gown trudges by me. She pushes a stainless-steel IV pole from which hangs a large bag of hideously yellow fluid. A tube parasitically enters beneath her gown. As she passes me, she flashes a smile full of chemotherapy-stained teeth, and I glimpse mysterious bruises and scars on her face and neck. I smile back at Joyce. She is one of my favorites.

Joyce has acute myelogenous leukemia. Despite a bone marrow transplant and the most intensive chemotherapy regimens we can offer, her disease has recurred twice. Her prognosis is bleak. During this stay she has brushed aside yet another serious infection that easily could have killed her. It still might in the months to come.

Our team of physicians gathers around Joyce's bed today, as we do for each patient on morning rounds. Some of the younger children here dread this part of the day. They whimper and frantically search for their mother, or lie still, sobbing, convinced that they will be subjected to some new unpleasantness. It hurts me each time I see these reactions, but I understand, and they are justified. Young children with cancer associate their physicians with the most terrifying and painful experiences they have ever endured. When they see me, they remember only the harsh chemotherapy that burns their veins, causes them to vomit for days, and makes them lose all of their hair. Or they remember the days of hip soreness following the time I forced anesthesia on them so that I could drive a needle into their bones to draw out marrow. Or they remember that each time they enter the hospital with a life-threatening fever, I get others to hold them down so that I can stick them with a needle to take their blood. They will never know that I have stayed up all night, fighting cancer and infection in their bodies with hours of careful monitoring. They will never know how much I might have come to care about them.

Joyce awaits the last person on our team to approach her bedside. She sits upright in her bed, pillows carefully propping her up, sheets and blankets neatly tucked in around her, as if she has been anticipating our arrival with great relish. "Which one of you doctors put me on this stupid diet?" she demands imperiously, addressing us with studied circumspection, as if holding court. We all burst into laughter. A small smile creeps into her face as she disdainfully directs her attention to a bowl of soggy rice in front of her. When we finish laughing, Don, a fellow resident and now the obvious culprit, timidly tries to defend himself, armed with a fatuous smile. "This is a special yummy diet we give all the kids when they have problems with going poo-poo too much, Joycey." Joyce scowls at Don. "Have you ever tried to eat rice for breakfast? You call that a breakfast!" We laugh again. I turn to Don. "Dr Daniels, how about letting Joyce have some real breakfast food, like Fruit Loops?" Joyce's eyes light up. "Yeah! Or an Egg McMuffin, or french fries. Get real, Dr Daniels!" It is obvious Don is a beaten man. As we file out, Don apologizes and assures Joyce of a more appetizing menu for lunch. As he leaves her room, she blurts, "OK, but don't forget, or you're in trouble!"

It's night. I'm on call. A nurse asks me to check on Joyce's complaints of pain. I find Joyce awake, sitting up in her bed in the dark, alone. Her mother frequently stays overnight in a recliner next to her bed, but she has gone home tonight. I can tell Joyce is awake by her movements, but until I reach the light I cannot discern her facial expression or mood. For a moment I feel in my gut a chill of desolation and sadness. I can only wonder what it is like to be a child of eight, alone in the darkness of a strange hospital, constantly reminded by pain, uncomfortable procedures, and other ravaged children that they have some gravely serious disease called cancer. Too many times the false comfort of narcotics is all these children have as they are insidiously devastated by the pain and progression of the disease.

I turn on the light. Joyce sits happily in front of me, smiling. My attention is drawn to the gold-speckled nail polish on her fingers and toes. "What's up?" I ask. "I have a little sore throat, and it's keeping me up." I am relieved. Maybe she just has a sore throat. I decide to examine her lymph nodes anyway. Her nodes are huge on both sides at the jaw angles and all over her neck. Indeed, any nodes I check are grossly enlarged. She is having a relapse on her last chance at a cure. I am upset but determined not to let it show. "Do you want some morphine for the pain? I already told your nurse that you can have it almost any time you need it." She replies without a pause, "Nah. Tylenol is fine. But don't give me any of that baby's Tylenol. I'm old enough to take

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From the Department of Pediatrics, New York Hospital-Cornell Medical Center, New York.
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pills, and they're always giving me that baby stuff. Why can't they just gimme a pill?" She violently emphasizes the last word while imploringly holding her open hands skyward, like a seasoned New York City cab driver. "Don't worry, Joyce, I'll make sure that the only Tylenol you get is a pill. No baby stuff for you." She flashes a little smile. I go to turn off the light above her bed, but she balletically flicks off the switch and lies down in one motion. "Oh, Dr Flores, don't forget that you guys promised me a real breakfast tomorrow." "No problem, Joyce. You can count on it. Just save me a little bit." I see her turn her head slightly in the dark. "Maybe. I'll think about it." I walk toward the doorway, and almost make it out. "Oh, Dr Flores!" she shouts. I turn and walk back in the room towards her bed. "What, Joyce?" She pauses momentarily. "Good night, Dr Flores." I reflect in the darkness. "Good night, Joyce."

My colleagues ask me why I like working with children with cancer. These children teach me about dealing with death. Children express feelings in the purest human form. They are not fettered by the propriety and repression of adults. I learn from the fearful children, the ones who sense death's imminence despite their parents' well-intentioned attempts at cover-ups. From them I reaffirm life's immediacy and vitality and how integral a part of life family is. And I learn from the determined strength of children like Joyce. They teach me that you must defy life's misfortunes with fundamental passions. Joyce's insistence on dignity is the flower that grows in spite of the desert.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

ONE CANDLE AND TWO RED BALLOONS

A black flame of resentment
Smolders in the twigs of passing years,
Crackles in the tall grass of middle age:

My son will never
Be one again,
And I am growing old.

His birthday candle
Flickered at blue icing
Just when the nurse called that night.

I had to go. We tried for hours
To save edematous lungs.
I went home almost as dead as them,

Found some colored paper, a ribbon,
Red balloons popped like shreds of pleura
Scattered in the quietness where my son slept.

I went to the kitchen,
Found a clean knife and plate,
Ate a piece of chocolate cake alone.

He is now grown, and
The old man died so much more easily
Than the memory of that one candle.

Yet I chose this work,
Would choose again this way
To become old myself.

ERIC DYER, MD©
Nashville, Tennessee

Dr. Craig Watson
Medical Director, Comprehensive Epilepsy Services
Sutter General Hospital

YOU CAN'T WATCH YOUR EPILEPSY PATIENTS ROUND-THE-CLOCK. BUT WE CAN.

Even if you've made a positive diagnosis of epilepsy in patients who are suffering from seizures, the most effective treatment is sometimes elusive.

The reason? Most physicians never directly observe a seizure. The patient usually recalls little, and second-hand accounts from family and friends are sketchy.

Sutter Neuroscience Center at Sutter General Hospital offers a comprehensive in-patient program for epilepsy that permits precise diagnosis and treatment.

Patients are monitored 24-hours a day by both video cameras and an EEG. When a seizure occurs, all relevant data can be recorded and studied. Treatment decisions, including medication and/or surgery, can then be based on specific information.

The four-bed unit, which is the largest and most complete in the region, is designed for the comfort of the patients, who may need to be hospitalized for up to a week. Rooms are outfitted with a television, VCR and personal exercise equipment.

The program is designed for patients aged fifteen and older who have tried several different anti-convulsant medications, yet continue to experience seizures that interfere with their quality of life.

Most insurance plans cover the costs. Once patients complete the program, they are returned to their primary care physician with follow-up recommendations.

For more about services or patient transfers, call Sutter Neuroscience Center at Sutter General Hospital in Sacramento, (916) 455-4323.

Sutter Neuroscience Center

INSTRUCTIONS FOR AUTHORS

Our readership represents all specialties of medicine. We wish to receive and publish manuscripts that are valid, important, lively, well-written, and succinct. They should be of interest to a broad range of busy practitioners, students, researchers, and scholars who have a clinical orientation. The purpose of a paper or letter may be to alert, review, discuss—above all, to teach. Titles should be short and intriguing. Avoid jargon, the overuse of abbreviations and acronyms, sexist language, redundancies, or expendable words and phrases (see *AMA Manual of Style,* 8th Edition).

Manuscript Information

Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, *The Western Journal of Medicine,* 221 Main Street, San Francisco, California 94105. Manuscripts must be original, not previously published, and not under consideration by another publication. If preliminary data were included in another presentation or publication, that should be noted in the cover letter and a copy of that publication should be included.

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Manuscripts, except for Case Reports, Epitomes, and Lessons From the Practice, should include an abstract of no more than 200 words summarizing the article. Abstracts should include a description of the purpose, design, patients, results, and conclusions.

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Research or project support should be included as a footnote to the manuscript or the accompanying cover letter.

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Acknowledgments

Acknowledgments will be printed on a select basis—to acknowledge those who contributed to but were not involved in the writing or review of the paper.

Preparation of Manuscripts

Everything, including references, tables, figure legends, and abstracts, **must be double-spaced.**

The original manuscript and two copies should be submitted on standard-sized heavy bond paper. Allow a margin of 2.5 to 4 cm (1 to 1.5 in) on both sides. Manuscripts transmitted by facsimile machine are not acceptable unless requested by the Editors.

All values should be in Système International (SI) units, with metric equivalents following in parentheses. Temperature readings should be given in Celsius. Use the generic name of drugs, with the salt or ester given when first used.

Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 × 17.8 cm (5 × 7 in) glossy prints, with the figure number, author's name, and top of the photo indicated with a label on the back. Patients (and relatives) have a right to anonymity in published clinical documentation. Details that might identify patients should be avoided unless essential for scientific purposes. Masking of the eye region in photographs of patients may be inadequate protection of anonymity. If identification of patients is unavoidable, informed consent should be obtained, and this should be clearly stated in the article. Changing data on patients should not be used as a way of securing anonymity. Figure legends, to be typed in sequence on the same page, should be in complete sentences. Any figures or tables previously published must be accompanied by a letter of permission to borrow from the copyright holder (the previous publisher). The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

All manuscripts will be subject to peer review to determine the originality, validity, and importance of con-

(Continued on Page 447)

THEY WERE CAREFREE...

They were raised in a simpler time, before sugar-free and fat-free. Now hypertension, often with elevated cholesterol and blood sugar, enters the picture...

NOW THEY'RE CONCERNED...

Today's hypertensives with new concerns...

THE CARDURA

*Adapted from the interim (12 months) results of the Treatment of Mild Hypertension Study, a randomized, double-blind, placebo-controlled trial of a nutritional-hygienic regimen along with various drug therapies. All drugs (except acebutolol) were given initially in low doses. If the patient showed a diastolic blood pressure more than 95 mm Hg on three successive follow-up visits, the dosage was doubled. If blood pressure remained elevated, a second drug (chlorthalidone, except for chlorthalidone group, which was given enalapril) was added. Mean diastolic blood pressure was lowered in various drug groups with median dosages, as follows: doxazosin (2 mg/day), 12.0 mm Hg; enalapril (5 mg/day), 12.2 mm Hg; chlorthalidone (15 mg/day), 13.1 mm Hg, and acebutolol (400 mg/day) 13.7 mm Hg (n=847; $P<0.01$ vs placebo).

†n=128, $P<0.01$ vs placebo. In a pooled analysis of placebo-controlled studies with about 300 predominantly normocholesterolemic patients per treatment group, CARDURA produced a small decrease in total cholesterol (-2.7%) and LDL cholesterol (-4.3%) and a small increase in the HDL/total cholesterol ratio (+4.3%).

‡Adapted from Lehtonen et al[2] (n=77; after 26 weeks: $P<0.001$ compared with week 0 for blood pressure and insulin, $P<0.05$ compared with week 0 for glucose).

GENERATION

Choose CARDURA: first-line therapy for a new generation of hypertensives.

Choose CARDURA for blood pressure control that doesn't jeopardize blood lipids.

In the Treatment of Mild Hypertension Study, CARDURA lowered diastolic blood pressure (mean 12.0 mm Hg) as effectively as enalapril, chlorthalidone, and acebutolol[1*]

CARDURA lowered blood pressure with a small increase in the HDL/total cholesterol ratio (+2.4%)* in the same study.[1†] The clinical significance of these changes is uncertain. Cholesterol is just one parameter to consider when selecting the best individualized therapy for a given patient

Choose CARDURA for blood pressure control that doesn't compromise blood sugar.

CARDURA controlled diastolic blood pressure without an adverse effect on glucose tolerance or insulin control[2‡]

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than placebo: dizziness, somnolence, and fatigue.[§]

Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo

§ These were generally mild and transient. Syncope has been reported, but rarely (<1%).

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

HYPERTENSION CONTROL FOR A NEW GENERATION.

Please see brief summary on last page.

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References: 1. The Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423. 2. Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. *Curr Ther Res.* 1990;47:278-284.

CARDURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg: about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR:	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES:	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL:	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.:	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL:	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY:	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

Bottles of 100: 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66).

Recommended Storage: Store below 86°F (30°C).

CAUTION: Federal law prohibits dispensing without prescription.

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tent and conclusions. Reviewers' comments will be returned with rejected manuscripts at the discretion of the Editors. All reviewers will remain anonymous. Any conflict of interest, actual or potential, will have been revealed to the Editors.

All accepted manuscripts are subject to copy editing, and the corresponding author is sent edited galley proofs for approval and necessary minor changes. Excessive changes at this stage may result in a delay of publication or withdrawal of the paper. No changes will be made after the final, edited version has been approved by the corresponding author without notifying the author. It is the corresponding author's responsibility to clear all corrections and changes with his or her coauthors.

Reprints

A form to order reprints will be sent to the author when the article is published.

References

All references should be cited in the text and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in *WJM* style per the examples given below.

(All references should be medical, scientific, or scholarly publications. Others—newspapers, magazines, etc—should be kept to a minimum and included in the text.)

Journal Articles

Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year).

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

CHECKLIST

- Original manuscript and 2 copies
- **Everything** double-spaced
- Illustrations, black and white glossy, identified with lead author's name—3 sets, plus figure legends that describe fully and in complete sentences what the figure depicts
- Letter of transmittal that includes release of copyright, statement of conflict of interest, and authorship responsibility, **signed by all authors**
- A 200-word abstract
- Title page that includes current affiliation of all authors and address **and telephone number** for corresponding author
- Permission-to-borrow letters for any previously published illustrations or tables
- All references numbered consecutively, double-spaced, and cited in text. No unpublished data or nonscientific publications listed in references (include in text)

(Continued from Page 368)

November 19-22—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

November 30-December 4—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

IDAHO

July 30-August 1—**Idaho Medical Association—Annual Meeting.** Coeur d'Alene. Thurs-Sat. Contact: Idaho Medical Assn, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 23-25—**14th Annual Cardiac Pulmonary Update.** Hyatt Regency Hotel, Albuquerque. Thurs-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

April 29-May 2—**Association of Veteran Administration Surgeons Annual Meeting.** Hilton Hotel, Albuquerque. Wed-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

April 29-May 2—**12th Annual UNM-ACP Emergency Medical Symposium.** Holiday Inn Pyramid, Albuquerque. Wed-Sat. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

May 14-15—**6th Annual Multicultural Mental Health Conference on Family and Children.** Hilton Hotel, Albuquerque. Thurs-Fri. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

May 15-16—**New Mexico Medical Society Annual Meeting.** The Marshall Building, Albuquerque. Fri-Sat. Contact: Glenn Taylor, New Mexico Medical Society, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

May 28-29—**3rd Annual Southwest Wound Care Symposium.** Holiday Inn-Pyramid, Albuquerque. Thurs-Fri. Contact: Diane Atchinson, PO Box 22569, Kansas City, MO 64113-0569. (816) 765-6644 or (800) 245-0372.

July 13-17—**Imaging 1992: Ultrasound, CT, MR, and Mammography.** Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 7-11—**Mammography Update.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

June 21-27—**School on Alcoholism, Drug Dependencies** (Sponsor: UUSM). Sun-Sat. U of U Browning Auditorium. Contact: UUSM.

June 24-27—**Slice of Life: Interactive Video and Related Multimedia Technology in Health Education** (Sponsor: UUSM). Wed-Sat. U of U Eccles Genetics Auditorium. Contact: UUSM.

July 12-17—**Update in Internal Medicine Focus on Ambulatory Care Medicine** (Sponsor: UUSM). Sun-Fri. Snowbird. Contact: UUSM.

August 6-8—**ISLD Dental Congress** (Sponsor: UUSM). Tues-Sat. Marriott Hotel, Salt Lake City. Contact: UUSM.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.
WRI:	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

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WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

April 17-18—**Tacoma Surgical Club.** Tacoma. Fri-Sat. Contact: PCMS.

April 24—**Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

April 24-25—**Diabetes of the Eye.** Seattle. Fri-Sat. Contact: U/W.

April 24-25—**Low-Back Pain.** Seattle. Fri-Sat. Contact: VMMC.

April 30-May 2—**Musculoskeletal Disease.** Seattle. Thurs-Sat. Contact: U/W.

May 1-3—**Radiology Annual Meeting.** Seattle. Fri-Sun. Contact: PNWRS, (206) 441-9762.

May 6-9—**Emergency Physicians Annual Scientific Assembly.** Seattle. Wed-Sat. Contact: WACEP, (206) 441-9762.

May 8—**Office Procedures.** Tacoma. Fri. Contact: PCMS.

May 13-15—**Fifth Conference on Occupational Hazards to Health Care Workers.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 15-16—**Medical and Orthopedic Issues of Active and Athletic Women.** Seattle. Fri-Sat. Contact: VMMC.

May 16—**Infectious Disease in Primary Care.** Seattle. Sat. Contact: U/W.

May 21-22—**Cardiology Conference.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

May 22-23—**Medicine Update.** Seattle. Fri-Sat. Contact: U/W.

May 27—**Pesticide Medicine.** Eastern Washington. Wed. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 28-30—**Musculoskeletal Disease.** Seattle. Thurs-Sat. Contact: U/W.

May 29-30—**Spinal Cord Injury.** Seattle. Fri-Sat. Contact: U/W.

May 30—**The Fetal Patient.** Seattle. Sat. Contact: VMMC.

June 11—**Endocrinology.** Everett. Thurs. Contact: PNMEI, (206) 258-6322.

June 12-13—**Urology.** Seattle. Fri-Sat. Contact: U/W.

June 18-20—**Diabetes Update.** Seattle. Thurs-Sat. Contact: U/W.

June 22-23—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: PCMS.

June 25-27—**Refocus on Women's Health Care.** Seattle. Thurs-Sat. Contact: U/W.

June 26—**Sports Medicine.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

July 23-26—**Current & Emerging Issues in Cancer Pain.** Seattle. Thurs-Sun. Contact: U/W.

July 29-31—**STD Update.** Seattle. Wed-Fri. Contact: U/W.

July 30-August 1—**STD Update.** Seattle. Wed-Fri. Contact: U/W.

August 3-8—**Summer Seminar in Medical Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 21-22—**Regional CME Network Meeting.** Seaside, Oregon. Fri-Sat.

September 14-18—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

September 23-24—**Critical Care.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

October 1-4—**Washington State Medical Association Annual Meeting.** Yakima. Thurs-Sun. Contact: WSMA.

October 15-17—**Endoscopic Sinus Surgery.** Seattle. Thurs-Sat. Contact: U/W.

October 22—**General Surgery Review.** Everett. Thurs. Contact: PNMEI, (206) 258-6322.

October 23—**Perinatology.** Fri. Tacoma. Contact: Multicare, (206) 594-1221.

November 12—**Dermatology.** Thurs. Everett. Contact: PNMEI, (206) 258-6322.

November 12-13—**Advances in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 20—**Orthopaedic Trauma Update.** Spokane. Fri. Contact: U/W.

December 4-5—**Urology Annual Meeting.** Vancouver, BC. Fri-Sat. Contact: NWUS, (206) 441-9762.

December 10-12—**8th Infectious Disease Conference.** Thurs-Sat. Everett. Contact: PNMEI, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 11-13—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

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SOUTHERN CALIFORNIA. FAMILY PRACTICE, BC, energetic individual for a rapidly growing three physician practice. Will need to do clinic, hospital, and long term care facilities. Excellent compensation, rapid progression to partnership. Location is 10 minutes from the ocean in a fast growing area near Oceanside. Here is a chance to practice private medicine without bureaucratic problems. Call (619) 630-2422.

INTERNAL MEDICINE RESIDENCY POSITIONS—R2 level. Available July, 1992. Excellent teaching with ample ambulatory opportunities. Inquire with CV to Stanton Siu, MD, or Denise Flaherty, MD, Medical Education, Kaiser Hospital, 280 W MacArthur Blvd, Oakland, CA 94611; or call (510) 596-6126.

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Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

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FAMILY PRACTICE, BC/BE to join group practice in growing southwestern town. Full service clinic, 280-bed hospital. Offering competitive salary, equal call schedule, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Linda Johnson, 8009 S. 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

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Tulare District Hospital
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PO Box 90112
Los Angeles, CA 90009
(800) 468-2687

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CALIFORNIA, PACIFIC NORTHWEST, ARIZONA. Positions in Family Practice, Internal Medicine, Orthopedics, Pediatrics and OB/GYN. Call or send confidential CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

UROLOGISTS—BC/BE needed for multispecialty group practice in central California and single-specialty group in Tucson, Arizona. Excellent compensation packages and partnership opportunity. All inquiries confidential. Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

SOUTHERN CALIFORNIA. Opportunity for part-time Emergency/Family Practice physicians at urgent care/industrial center in Orange. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled Family Practice physician to join our highly respected Urgent/Primary Care group with two beautiful Santa Cruz clinics. Flexible scheduling and a comprehensive benefit package. Rapid advancement to full partnership. Please send CV to Stuart Simon, MD, 6800 Soquel Dr, Aptos, CA 95003 and call (408) 662-3611.

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BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

BC/BE GENERAL INTERNIST NEEDED. Nine physician department in 27 doctor multispecialty clinic. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

(Continued on Page 452)

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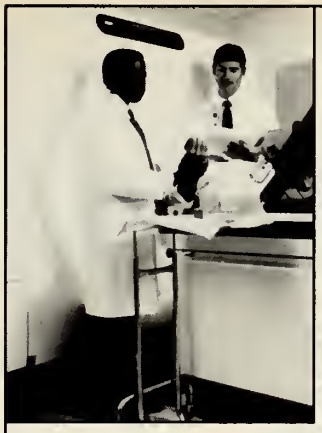

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AIR FORCE

(Continued from Page 451)

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HAWAII. FAMILY PRACTITIONER, INTERNIST, AND PEDIATRICIAN NEEDED for rural underserved area. Full-time position in nonprofit community health clinic. Desire dedicated person to work in multicultural setting. Contact Kathy Garner, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-1458.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

SEATTLE, WASHINGTON. PACIFIC MEDICAL CENTER has Family Practitioner positions, BC/BE, available at three of its six neighborhood clinics. PMC is a growing, Primary Care-based, multispecialty organization with extremely well run, well equipped clinics that provide many ancillary services. Most of the clinics are located within one mile of a major hospital. PMC offers its providers a balanced life-style, competitive salaries, and an excellent benefit package that includes paid malpractice. The greater Seattle area offers year-round outdoor recreation including, skiing (snow/water), hiking, boating, and fishing at numerous lakes, national parks, and in Puget Sound. Send CV to Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4100.

AMBULATORY CARE, Hayward, Modesto, Orange County, California. Thriving practices, attractive facilities, competitive salary, profit-sharing, partnership with growth potential. Contact Robin Morgan, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612; (510) 835-7431. Outside of California, (800) 842-2619.

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EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

MONTEREY. MULTIDISCIPLINARY, four physician clinic. Immediate need for Family Practice/Internal Medicine. Progressive modern clinic: Industrial, private, and personal injury. Pat Callow, 550 Camino El Estero, Ste 204, Monterey, CA 93940; (408) 375-5151.

PHYSICIANS WANTED

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full-/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

BEAUTIFUL OREGON COAST. Private multispecialty cooperative with excellent facility seeking Family Practice physician to join five full-time Family Practitioners. Full spectrum of Family Practice. In-house lab, x-ray, day surgery. Contact Marce Knight, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294 or (800) 234-1231.

CALIFORNIA MULTISPECIALTY. Dermatologist, Radiologist, Otorhinolaryngologist, General Surgeon, Cardiologist, Internal Medicine, Pediatrician, Gastroenterologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

OB/GYN—Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE Physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

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(Continued from Page 452)

PHYSICIANS WANTED

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GENERAL INTERNIST in the Pacific Northwest. Busy 30 physician multispecialty group practice looking for General Internist with ICU skills and interests to join existing Internal Medicine department. Competitive salary and benefits. Send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

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NORTHERN CALIFORNIA—FAMILY PRACTICE FACULTY. Vigorous, growing program with rural emphasis, in Shasta-Cascade recreation area seeks residency trained BC/BE Family Physician to join core faculty team. Practice, teaching, and OB experience desirable. Responsibilities include teaching and direct patient care in hospital, FPC and coordination of R-1 curriculum. UC Davis affiliate program trains 18 residents in 254-bed regional referral center. Clean air, good schools, four-season recreation. Send CV to Perry Pugno, MD, Program Director, 2615 Breslauer Wy, Redding, CA 96001; (916) 246-5716.

NORTHERN CALIFORNIA-FACULTY INTERNIST. Vigorous, growing Family Practice residency with rural emphasis in Shasta-Cascade recreation area seeks residency trained BC/BE Internist to join core faculty team. Practice and teaching experience desirable. Responsibilities include teaching and direct patient care in hospital and clinic. Clinical research encouraged. UC Davis affiliate program trains 18 residents in 254-bed regional referral center. Clean air, good schools, four-season recreation. Send CV to Perry A. Pugno, MD, Program Director, 2615 Breslauer Wy, Redding, CA 96001; (916) 246-5716.

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BC/BE FAMILY PRACTITIONER for satellite clinic of prestigious multispecialty group practice. Join one other Family Practitioner and one Physician's Assistant in small town setting with urban culture 20 minutes away. Generous benefit package. Send CV to Donald Benz, MD or Karen Stanton, The Vancouver Clinic Inc, PS, 700 NE 87th Ave, Vancouver, WA 98664; (206) 254-1240.

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MAJESTIC SKAGIT VALLEY IN WESTERN WASHINGTON has multispecialty group seeking eighth Family Practitioner. BE/BC, OB optional. Competitive salary and benefits. If interested, send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

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MARIN COUNTY. BC/BE noninvasive Cardiologist needed to join two Cardiologists in a 25 physician department of Internal Medicine. Growing pre-paid group practice in San Rafael, California; 10 miles north of San Francisco. Satellite medical offices in Novato and Petaluma. Competitive salary and excellent benefits. Please send CV to Frank E. Jeffrey, MD, Chief, Cardiology, The Permanente Medical Group, Inc, 99 Montecillo Rd, San Rafael, CA 94903. EOE.

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Internist wanted for beautiful Salt Lake City area. Excellent skiing, camping, fishing and hunting. Looking for aggressive, hard-working Family Practitioner to expand clinic. Complete laboratory facilities and x-ray in ambulatory care type setting. Call or write: **Robert Davis, MD, Director, Family Medical Center, 1519 W. 9000 South, West Jordan, UT 84088; (801) 562-9100.**

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FAMILY PRACTICE. Private practice opportunities available in Reno/Sparks, Nevada; Las Vegas, Nevada; Seattle, Washington suburb; Texas, Louisiana, and Florida. For details, call Eloise Gusman; (800) 535-7698, or send CV to PO Box 101656, Fort Worth, TX 76185.

INTERNAL MEDICINE. Practice opportunities available with established physicians in Seattle, Washington suburb; Reno/Sparks, Nevada; Victoria and McAllen, Texas; New Orleans suburbs and Shreveport, Louisiana; West Palm Beach, Florida, Plantation, and Hollywood, Florida. For details, call Eloise Gusman; (800) 535-7698, or send CV to PO Box 101656, Fort Worth, TX 76185.

CALIFORNIA, BERKELEY. Experienced Emergency Room, Family Practice, Internal Medicine, and Urgent Care Physicians sought to staff an inpatient service at a large community hospital. Excellent hours (no nights) and compensation. Applicants must be BC/BE in either Emergency Medicine, Family Practice, or Internal Medicine. Job parameters may be configured to accommodate full- or half-time commitments. Please send CV to Joan Wendell, Office Manager, PO Box 5138, Berkeley, CA 94705.

ANESTHESIOLOGIST, BC. Immediate half-time position in Pocatello, Idaho (50,000 population). Join four MDs and seven CRNAs. All specialties except Cardiac. Full benefit package. Excellent hunting, fishing, and skiing. Home of Idaho State University. Contact Philip J. Knox, MD; (208) 234-1363, 7727 Katsilometes, Pocatello, ID 83204.

ORTHOPEDIC SURGEON. University of California, San Francisco seeks a BC/BE Orthopedic Surgeon to fill a faculty/staff position at the Valley Medical Center, Fresno. The Orthopedic Department at VMC supports a busy trauma service and actively participates in teaching residents in General Surgery, Emergency Medicine, and Family Practice. This position also offers private practice opportunities in a setting within the faculty group. Competitive salary and benefits. The central California location offers affordable and enjoyable year-round recreational living. Address inquiries and CVs to Louis Conway, MD, Acting Chief of Orthopedics, 4910 E Clinton, #101, Fresno, CA 93727. EO/AA employer, women and minorities are encouraged to apply.

(Continued on Page 455)

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MULTIDISCIPLINARY PAIN CENTER in Portland, Oregon seeks full-time physician, BC/BE Neurologist, Physiatrist, or Orthopedist, with interest in chronic pain, psychosocial aspects of medicine, working as part of a multidisciplinary team. Send CV to Janet E. Ploss, MD, Emanuel Pain Center and Worker Services, 3001 N Gantenbein, Portland, OR 97227; FAX (503) 280-4119.

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INTERNIST. BE/BC Internist wanted as associate for solo practitioner in San Luis Obispo County. Growing medical community offering a tremendous quality of living; award winning local wineries, recreational lakes and beautiful oak-studded hillsides. Income guarantee. Contact Steven J. McAllen, MD, 959 Las Tablas Rd, Ste B2, Templeton, CA 93465; phone (805) 434-1166.

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CALIFORNIA. PALM SPRINGS AREA. BC/BE Emergency or Family Practice physician for growing, state-of-the-art Urgent Care clinic. Paid malpractice. Salary plus profit sharing. Contact Govind Sharma, MD, FACEP, Palm Desert Urgent Care, 73-345 Hwy 111, Palm Desert, CA 92260; (619) 340-5800.

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San Francisco Department of Public Health
25 Van Ness Ave, Ste 500
San Francisco, CA 94102; (415) 554-9010
For information: Judith Hager, MPH
HC #1 Director; (415) 554-9765

CONTRACT MEDICAL CONSULTANT, EL CENTRO, CALIFORNIA. The California State Department of Rehabilitation is recruiting for the position of Medical Consultant. Physician to provide medical consultation including reviewing medical records, documenting disabling conditions, recommending work limitations, and consulting with Rehabilitation Counselors regarding DR clients. There is no direct patient contact. Contractor will be required to work eight (8) hours per week at the El Centro Branch Office, and will be paid $40.00 per hour. The contract duration will be twelve (12) months with a possible two (2) year renewal. Must be currently licensed to practice medicine in California and no disciplinary action pending. Interested parties should submit a résumé by 5 pm, April 25, 1992, to Bruce K. Smyth, Department of Rehabilitation, 6848 Magnolia Ave, Ste 5, Riverside, CA 92506. The State of California is an Affirmative Action Employer.

PRACTICE IN SAN DIEGO. BE/BC Family Practitioner or Internist needed for busy private practice opportunity leading to partnership. Competitive salary and compensation package. Beautiful San Diego lifestyle. Send CV to Joseph Browne, MD, 1809 National Ave, San Diego, CA 92113; or call (619) 234-8171, ext 311.

TWO FULL-TIME MD POSITIONS AT THE LEVEL OF ASSISTANT/ASSOCIATE PROFESSOR OF FAMILY PRACTICE available in the Family Practice Department, University of California, Davis. Must be BC by the American Board of Family Practice with interest, training, and/or experience in research, academic publication, administration, teaching, and obstetric activities. The positions will remain open until June 30, 1992. Send CV with list of four references to Klea Bertakis, MD, Department of Family Practice, UC Davis, 2221 Stockton Blvd, Sacramento, CA 95817. The University of California is an affirmative action, equal opportunity employer.

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We offer competitive salary, a comprehensive benefits package including retirement and 401K plan contributions, and early access to partnership and stockholder status.

The South Bay area provides a wide range of cultural and recreational activities, good schools, fine dining, and a congenial climate.

If you are committed to excellence and strongly motivated for success, we'd like to hear from you. Send your CV to Maureen Forrester, San Jose Medical Group,* 45 S 17th St, San Jose, CA 95112; or **call (408) 282-7833.**

*An independent physician group affiliated with Stanford University Medical Center

WANTED: PHYSICIAN ADMINISTRATOR. NEW MEXICO. The Los Lunas Hospital and Training School, a 350-bed state operated facility for persons with developmental disabilities, is currently recruiting for a Physician Administrator. Located approximately 20 miles south of Albuquerque, New Mexico, we provide professional services and patient care to mentally and physically disabled clients. The job entails responsibility for general, technical direction of all service related to patient care and professional operations. Minimum qualifications include graduation from an accredited medical school and completion of an approved internship, plus four years experience in the practice of medicine, and licensure by the New Mexico Board of Medical Examiners. Salary up to $78,404 per year plus benefits; medical malpractice provided by the facility. Direct inquiries to David LaCourt, PhD, Administrator, Los Lunas Hospital and Training School, PO Box 1269, Los Lunas, NM 87031; (505) 841-5264.

WARM AND SUNNY ARIZONA. Thomas-Davis Medical Centers, an expanding multispecialty group of 170 plus physicians, needs Pediatrics, Internal Medicine, Family Practice, OB/GYN, Urgent Care, General Surgery, Orthopedic Surgery, and Retina specialists. Top benefits, profit sharing, guarantee first two years, plus incentive pay, early shareholder. Fee-for-service plus HMO. BE/BC. Call or write Bill De Long; (800) 658-9166, TDMC, PO Box 12650, Tucson, AZ 85732.

(Continued on Page 456)

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ACADEMIC GENERAL INTERNIST

The University of Utah School of Medicine, Division of General Medicine is offering full-time positions for BC/BE Internists at the Instructor, Assistant Professor, Associate Professor levels. Rank and salary commensurate with qualifications. Opportunities include patient care, teaching of medical students and residents, administration, and clinical research. Applications must be postmarked by May 31, 1992; applications submitted after the deadline may be considered if no qualified candidates have applied by that deadline. An equal opportunity employer. Contact John H. Holbrook, MD, Department of Internal Medicine, University Hospital 4B-120, Salt Lake City, UT 84132.

EASTERN WASHINGTON. Position available for Family Physician in beautiful eastern Washington rural area. Salary income, malpractice paid, and a complete benefit package. Call or send CV to Inland Empire Personnel Service, Mike Nation, Physician Placement Director, N. 4407 Division, Ste 500, Spokane, WA 99207; (509) 484-3266.

ACADEMIC PULMONOLOGIST/INTENSIVIST. Academic Pulmonary/Critical Care physician needed to join a three physician division of Respiratory and Critical Care Medicine at a 400-bed teaching hospital with Stanford University affiliation. The hospital has a full Internal Medicine residency training program and the division is part of a combined three hospital Pulmonary fellowship (SCVMC, Stanford University, and Palo Alto VA). The division's activities include supervision of medical students, residents and fellows, direction of a complete PFT LAB and an eight-bed MICU and participation in clinical research. Address inquiries to Carl M. Kirsch, MD, Division of Respiratory and Critical Care Medicine, Santa Clara Valley Medical Center, 751 S. Bascom Ave, San Jose, CA 95128; or call (408) 299-5514. An equal opportunity and affirmative action employer.

NORTHERN CALIFORNIA'S NUMBER ONE IMMEDIATE CARE medical center is currently seeking a motivated physician with Emergency/Family Practice experience to join our team. A college town, very attractive compensation, and location, are just a few of the things that make this position unbeatable. Please contact Francine Marquis; (916) 891-1676.

NORTHERN CALIFORNIA RECREATION AREA. Full-time and part-time salaried position in Ambulatory Care clinic. Enjoy excellent working hours, no night call, generous benefits package, malpractice insurance provided. Located near the Sierra foothills offering excellent opportunities for hiking, swimming, boating, fishing, and skiing. California license required. Family Practitioner preferred. Call or send résumé to Northern Valley Indian Health, Inc, 2167 Montgomery St, Oroville, CA 95965; (916) 534-8440. EOE. Native Americans encouraged to apply. Deadline: June 1, 1992.

CALIFORNIA MEDICAL/LEGAL DISABILITY EVALUATIONS. Opportunities available in San Jose, San Ramon, Fremont, and Capitola, California for BC physicians in Orthopedics, Psychiatry, and Cardiology with multispecialty forensic medical evaluation group. Practice limited to evaluations. California license required. Excellent opportunity to supplement income. Send inquiry and CV to Martie Woodson, QMA, 2131 The Alameda, San Jose, CA 95126.

NORTHERN CALIFORNIA—SOUTH BAY

BC/BE Family Physicians and Internists needed for:

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All positions offer competitive compensation packages. For additional information please send CV to **Jan Sturges, Medical Management Services, 532 Race St, San Jose, CA 95126.**

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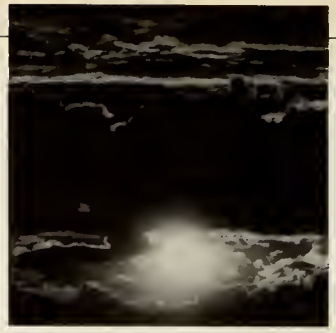

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If you are committed to excellence and strongly motivated for success, we would like to hear from you. Please send your CV to Maureen Forrester, San Jose Medical Group, Inc, 45 S 17th St, San Jose, CA 95112; **or call (408) 282-7833.** An independent physician group affiliated with Stanford University Medical Center.

CARLSBAD, NEW MEXICO. SEEKING BE/BC OB/GYN to purchase existing successful solo private practice in southeastern New Mexico. Different purchase options available from equipment only to complete office setup and integration. 138-bed hospital and level II Nursery. Two other OB/GYN physicians available for possible call sharing. No HMOs or PPOs. Claims made malpractice available. Pleasing community atmosphere. Close to National Park and Forest, lake, and water sports. Two hours from ski area. Smog free and pleasant desert climate. For information call (505) 885-1162 or send CV to S. Schneberger, MD, FACOG, 2402 W. Pierce, #6F, Carlsbad, NM 88220.

PHYSICIAN—BC/BE Medical Director, Family Practice/General Medicine in small Native American Health Clinic. Northern California, beautiful mountains, rivers, close to coast, in wine and redwood country. Good schools, quality lifestyle. Congenial, progressive medical community, salary competitive. CV to Sue Meyer, 564 S. Dora St, Ste D, Ukiah, CA 95482; (707) 468-5341.

PHYSICIANS WANTED

TRINIDAD, CALIFORNIA

Private Indian clinic overlooking ocean on northern California coast seeking two BC/BE Family Physicians to join two other Family Physicians. Exciting, challenging, comprehensive program, including Obstetrics. Gael Dougherty, RN, Medical Department Coordinator, UIHS, PO Box 420, Trinidad, CA 95570; (707) 677-3693.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

GENERAL INTERNIST—BE/BC needed to join me in my successful, rapidly expanding practice in a beautiful new office in southern Marin County. Part-time position available immediately, leading to partnership. Must be US university trained, willing to work hard, ambitious, and desiring a solid future practice. Submit CV to PO Box 880, Larkspur, CA 94977-0880.

EXCELLENT OPPORTUNITY for a Gastroenterologist familiar with the newer GI procedures to join two established Gastroenterologists in the greater Sacramento area. If interested please send CV to PO Box 2304, Fair Oaks, CA 95628.

(Continued on Page 457)

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PHYSICIANS WANTED

OHIO, WISCONSIN, MISSOURI

Attractive opportunities in metropolitan and scenic recreational areas. Locations near pristine lakes, white water rivers, and national forests. Others in college communities offering professional and Big 10 college sports, fine arts, and a broad spectrum of nationally renowned CME programs. Positions available: Allergy, Dermatology, Neurosurgery, Occupational Medicine, Oncology, Orthopedics, Psychiatry, Rheumatology, and Urology. To discuss your practice preferences and these opportunities please call our toll-free number, (800) 243-4353, or send your CV to STRELCHECK & ASSOCIATES, INC, 10624 N. Port Washington Rd, Mequon, WI 53092.

SAN JOSE. Multispecialty Primary Care group practice needs BC/BE physicians for Family Practice, Pediatrics, Internal Medicine and OB/GYN. Generous salary, benefits, and livable practice schedule are offered to qualified candidates. Affiliation with progressive 200-bed hospital. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411; FAX (415) 399-0411.

NEW MEXICO. Excellent opportunity for BC/BE OB/GYN, Internal Medicine, and Family Practice to join successful practices or start new in a growing community. Plan on full practice from the beginning. Enjoy sunshine, skiing, hiking, fishing, and hunting in a southwestern lifestyle. For further information on benefits and compensation contact Anne Winter, RN, Director of Professional Development, St Joseph Healthcare System, Albuquerque, NM; (505) 246-8003.

PEDIATRICIANS—Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

BE/BC FAMILY PRACTITIONER to join one Family Nurse Practitioner, one Pediatric Nurse Practitioner and one OB/GYN Nurse Practitioner, and two part-time OB/GYNs in Walla Walla, Washington. Share call with four practitioners. Competitive salary, excellent benefit package, including vacation up to 32 days per year and professional liability. Public Health Service immediate Loan Repayment slot. Contact Sylvia Arroyo, Clinic Administrator, Family Medical Center, PO Box 515, Walla Walla, WA 99362; (509) 525-6650, or Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant; (509) 865-5898.

MONTEREY BAY. Midway between Santa Cruz and Monterey, this unpretentious community is perfect for the hiker, biker, surfer, and outdoorsperson. Medical staff is cohesive and anxious to welcome additional Family Physicians, Pediatricians, and General Internists. Group and independent practice with call schedules which allow time for lifestyle. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

GASTROENTEROLOGY—SAN DIEGO. Excellent opportunity to expand present practice or start new one. Confidentiality respected. Collections $350,000. Excellent profits. Greater than 50% private patients. Call Marc Miller; (310) 430-3430.

FAMILY PRACTITIONERS/OB/GYNS. California association coordinating recruitment efforts for 200 plus community clinics in state can place you in rural or urban region. Large or small practice. Varying but competitive compensation; all cover malpractice. CV and letter stipulating preferred region of state to ACHC, 1025 Ninth St, Ste 213, Sacramento, CA 95814; (916) 448-6001.

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FAMILY PRACTITIONER FACULTY/DIRECTOR OF GERIATRICS needed at community USC/LLU affiliated residency in suburb 15 minutes from downtown Los Angeles, mountains, and Pasadena. Excellent salary and benefits. Send CV to Jack Yu, MD, 801 S. Chevy Chase Dr, #201, Glendale, CA 91205; (818) 500-5594.

DERMATOLOGIST. Immediate opportunity available for full- or part-time position with University affiliated multispecialty group in one of the most desirable cities. We offer a balanced lifestyle, competitive salary and an excellent benefit package. Send CV to Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

CALIFORNIA. The Sacramento Children's Medical Clinic, an ambulatory private practice for children of low income parents, consisting of four offices (one on wheels) needs a BE/BC General Pediatrician. Direct patient care and supervising midlevels for inner city, migrant health and outreach programs. Monday through Friday. Quake-free locale. Spectacular climate. Innumerable recreational opportunities. Competitive salary with equity potential. Contact Gilbert Simon, MD, 1355 Florin Rd, Ste 14, Sacramento, CA 95822, (916) 422-6326.

NEED ASSOCIATE to join busy dermatology practice in Santa Barbara, California. Will also consider sale at a reasonable price. Excellent opportunity to live in a beautiful seaside community. Call Dr Senn at (805) 569-0186 or evenings at (805) 565-3908.

FAMILY PHYSICIAN—SAN FRANCISCO BAY AREA. Small Family Practice group in Alameda seeks BC/BE Family Physician to join thriving practice. No OB. Contact Peter Candell, MD, Alameda Family Physicians; (510) 769-9492.

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BC/BE OB/GYN with commitment to caring for the underserved, needed to join 13 physician (OB, Family Practitioner, Pediatrics, Internal Medicine) Primary Care community health clinic in Toppenish, Washington. Rural setting, beautiful, sunny, central Washington near Columbia River gorge. Diverse cultural influences (Hispanic and Native American). Recreational opportunities including fishing, skiing, and bikers' paradise. Competitive salary with excellent benefit package including vacation up to 32 days per year and paid professional liability. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

BC/BE FAMILY PHYSICIAN to join three other Family Practitioners, OB/GYN, Internist, and Physician Assistant at busy Migrant/Community Clinic in Grandview, Washington. Full-range Family Practice, including Obstetrics, hospital work, and Emergency coverage. Excellent relationship with well trained BC Family Practitioners and surgeon in community. Friendly rural area with good schools. Close to mountain recreational areas and water sports. Professional liability paid. Excellent benefits, vacation liberal. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

BC/BE OB/GYN to join one Internist, one Family Nurse Practitioner, one Pediatric Nurse Practitioner, and one OB/GYN Nurse Practitioner in Walla Walla, Washington. Shared call with two local OB/GYNs. Competitive salary, excellent benefit package, including vacation up to 32 days per year and professional liability. Public Health Service immediate loan repayment slot. Contact Sylvia Arroyo, Clinic Administrator, Family Medical Center, PO Box 515, Walla Walla, WA 99362; (509) 525-6650, or Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant; (509) 865-5898.

BC/BE FEMALE INTERNIST sought to join established female Internist in a southern California private practice. Send CV to Number 261, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ESCAPE those urban hassles and come to scenic northern California. Opportunity available to join two other Internists in private practice. Competitive salary and benefit package available. Contact Mark Oswald of Gielow/Laske Associates, Inc, 306 N Milwaukee St, Milwaukee, WI 53202; (800) 969-7715, FAX (414) 226-4131. Confidential inquiries welcome.

WANTED: CLINICIAN/TEACHER to join 15 General Internists at Santa Clara Valley Medical Center and Clinics, a public hospital affiliated with Stanford University. Applicants should be BE (BC if eligible more than two years), love clinical medicine and patient care, enjoy housestaff and medical students, and have excellent sense of humor to deal with usual politics of university-affiliated public hospital/clinic work. Send inquiries, CV to Kent Imai, MD, Chief, Primary Care Division, Department of Medicine, Santa Clara Valley Medical Center, 750 S Bascom Ave, San Jose, CA 95128.

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FULL-TIME PAY/PART-TIME WORK. 116K plus two weeks on, 2 weeks off, malpractice, and overhead paid. Churchill Community Hospital in Fallon, Nevada is looking for an Emergency Room Physician to work a block schedule. ACLS, ATLS, Primary Care BE. 10,000 patients per year serving one large rural area. Located 60 miles east of Reno and the Lake Tahoe area. Other practice opportunities also available. Contact Betty Kuffel, MD, ED, or Jeffrey Feike, Administrator; (702) 423-3151.

PREVENTIVE MEDICINE RESIDENCY candidates sought. Two year program includes MPH degree and practicum leading to BE in General Preventive Medicine. Especially interested in individuals with in-skill development for health promotion and disease prevention for medically underserved populations. Boards in Internal Medicine/Family Practice/Pediatrics desired but not necessary. Salary $30,000 plus fringes. Please write/call Kevin Patrick, MD, MS, Director, University of California, San Diego—San Diego State University General Preventive Medicine Residency Program. San Diego State University, San Diego, California 92182-0567; or phone (619) 594-5332 or FAX to (619) 594-5613.

SEATTLE. As the result of population growth and reputation, this 28 physician group practice is in need of several recently trained Family Practitioners. This suburban community is situated within minutes of downtown Seattle and within one hour of Mt. Rainier. Remuneration package includes base salary plus incentive and full benefits with partnership after two years. Call rotation every 7th night and weekend. Congenial atmosphere. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

BC/BE FAMILY PHYSICIAN needed to join solo Family Practitioner, president of a 13 physician IPA in thriving, established practice located in Gilroy, California. Practice includes the full range of Family Medicine, excluding OB. Enjoy the relaxed, family-oriented community that is just 25 miles south of San Jose. Good call coverage exists. Call Jan Sturges at (408) 999-7110, or send CV to MMS, 532 Race St, San Jose, CA 95125.

EXCELLENT OPPORTUNITY FOR BC/BE INTERNIST to join four Internists in San Jose area with future opportunity to assume practice of retiring physician(s). Exceptional income guarantee and benefit package being offered. Interested candidates call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

BC/BE FAMILY PHYSICIANS needed for large multi-specialty group in San Jose, California. Continuing Care and Urgent Care available. Family Practice Department includes Internal Medicine, Pediatrics, Gynecology, minor surgery with inpatient/outpatient responsibilities. Good call coverage exists. Competitive salary and benefits offered. Call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

SAN FRANCISCO BAY AREA. Palo Alto Medical Clinic, a 150 physician multispecialty group with a national reputation for innovation and excellence, seeks BC/BE Family Practice physician to join vigorous eleven member department. Exciting opportunity for energetic person to become part of innovative health care team. Competitive salary based on experience. Excellent benefits package. Two year partnership track. Please forward letter of interest and CV to George Perlstein, MD, Medical Director, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

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PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (510) 601-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

NORTHERN CALIFORNIA COAST. Seven physician Primary Care group located behind the Redwood Curtain seeks an additional BC Internist. We are looking for someone who will enjoy practicing high quality medicine far from the urban rat race. Arcata is a small coastal university town which we feel combines the best of rural lifestyle in a cosmopolitan environment. Send CV to Arcata Family Medical Group, 4555 Valley West Blvd, Arcata, CA 95521.

PUGET SOUND. Internist to share equipment, office, and call in high growth community 30 minutes north of Seattle. We seek a fourth physician eager to maintain independent practice and finances, to share expenses and reduce starting costs by first year use of computer, phone, ECG, etc. Buy in later. Ample patient base. Excellent medical community and full service hospitals. Maximal scheduling freedom, but would make own practice management decisions. Well located new office. Contact J. Shaw, MD, 1330 Rockefeller, Ste 210, Everett, WA 98201.

FAMILY PRACTICE—NORTHERN CALIFORNIA BC/BE. Immediate opportunity for an associate. All negotiable proposals considered. Advance to partnership in very lucrative and exciting practice located 30 miles east of San Francisco next to 300-bed hospital. Send CV to Fred Von Stieff, MD, Mount Diablo Hospital, 2540 East St, Concord, CA 94520; (510) 680-8933.

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FOR SALE. Established, busy Urology practice in southwestern New Mexico. No investment required. Excellent year 'round climate and outdoor recreational opportunities. Call collect, Pierson Deming, MD (505) 388-1561 (office) or (505) 388-4557 (home): or call Steve Jacobson, Administrator, Gila Regional Medical Center, (505) 388-1591.

FAMILY PRACTICE FOR SALE. Utah's most desirable place to live. High mountains, clean air, and 15 minutes to the west's three greatest ski resorts; Park City, Park West, and Deer Valley. Great schools and rural atmosphere but adjacent to Salt Lake City, Provo, and Park City. One of the few areas with Family Practitioners doing own general surgery/deliveries. Present physician retiring. Zero down. 10 year payoff. J. D. Boggess, MD, Heber, UT 84032; (801) 654-3535.

AVAILABLE FOR SALE. General Surgery, hospital based practice. Colorado Springs, Colorado. 25 E Jackson, Ste 305, Colorado Springs, CO 80907; (719) 636-0075; FAX (719) 636-0070. Sale includes Penrose Hospital office lease, equipment, patient records, managed care contacts, and referral base.

OAKLAND/BERKELEY, CALIFORNIA. High quality OB/GYN practice for sale. Located in beautiful Victorian building. Close to two major hospitals. Available 1992. Terms negotiable. Contact Hilary Modell; (510) 420-1200.

ESCAPE TO NORTH IDAHO. Six year General/Internal Medicine practice for sale. Gross $260,000. Located in Kellogg, Idaho. Silver Mountain ski area is minutes from office. Quality family lifestyle, excellent business opportunity. Very reasonably priced; (208) 682-4876 (home).

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SAN DIEGO COUNTY. Family, Internal, OB/GYN, and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

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LOCUM TENEN. BE/BC OB/GYN to cover leave of absence for two of our regular staff Obstetricians. Coverage needed June to August 1992. Friendly rural area close to mountain recreational opportunities and water sports. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 856-5898.

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Hypersensitivity to minoxidil, propylene glycol, or ethanol.

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1. *Need for normal scalp:* Before starting treatment, make sure that the patient has a normal, healthy scalp. Local abrasion or dermatitis may increase absorption and hence the risk of side effects.

2. *Potential adverse effects:* Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption because of misuse, individual variability, or unusual sensitivity could, at least theoretically, produce a systemic effect.

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Potential patients should have a history and physical and should be advised of potential risks. A risk/benefit decision should be made. Heart patients should realize that adverse effects may be especially serious.

Alert patients to the possibility of tachycardia and fluid retention and monitor for increased heart rate, weight gain, or other systemic effects.

PRECAUTIONS

General Precautions: Monitor patients 1 month after starting ROGAINE and at least every 6 months thereafter Discontinue ROGAINE if systemic effects occur.

The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eyes, abraded skin, and mucous membranes), bathe with copious cool water.

Avoid inhaling the spray.

Do not use in conjunction with other topical agents, such as corticosteroids, retinoids and petrolatum, or agents that enhance percutaneous absorption.

ROGAINE is for topical use only. Each mL contains 20 mg minoxidil, and accidental ingestion could cause adverse systemic effects.

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Patient Information: A patient information leaflet is included with each package and in the full product information.

Drug Interactions: No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice In rats, there was a dose-dependent reduction in conception rate.

Pregnancy Category C: ROGAINE should not be used by pregnant women.

Labor and Delivery: The effects are not known.

Nursing Mothers: ROGAINE should not be administered to nursing mothers

Pediatric Use: Safety and effectiveness has not been established for patients under age 18.

Postmenopausal Use: Efficacy in postmenopausal women has not been studied

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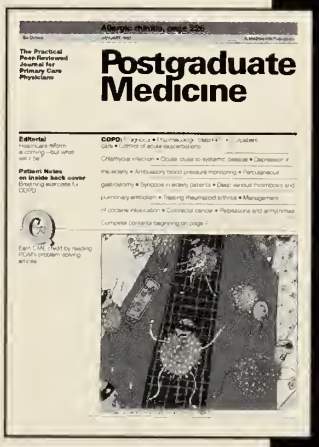

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WILLIAM A. SEE, MD, and RICHARD D. WILLIAMS, MD
From the Department of Urology, University of Iowa Hospitals and Clinics, Iowa City.

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‡Verapamil should be administered cautiously to patients with impaired renal function.

References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade: Verapamil in Focus.* New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol.* 1990;66:131-151. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow-release verapamil in essential hypertension. *Eur J Clin Pharmacol.* 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation.* 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology.* 1988;39:1025-1029.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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Items of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently became reasonably firmly established, both as to scientific fact and important clinical significance.

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From the Fred Hutchinson Cancer Research Center, Cancer Prevention Research Unit, and the University of Washington Schools of Public Health and of Medicine, Seattle; the Department of Medicine, University of California, San Francisco; the Department of Medicine, Yale University, New Haven, Connecticut; Kaiser Permanente Center for Health Research, Portland, Oregon; the Department of Medicine, University of Maryland, Baltimore; and the Department of Medicine and Cancer Center, University of California, Irvine, Orange.

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JOSEPH LA DOU, MD

From the Division of Occupational and Environmental Medicine, University of California, San Francisco, School of Medicine.

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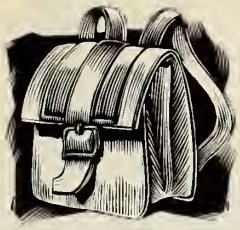

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Dr Reeders is Associate Investigator, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, Connecticut.

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Dr Garnick is Vice President, Clinical Development, Genetics Institute, Cambridge, and Associate Clinical Professor of Medicine, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts.

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups.The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, dilatation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared on treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups when the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes on baseline and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency in patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and arthralgia related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

June 4-6—**Arizona Medical Association—Annual Meeting.** Scottsdale. Thurs-Sat. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 17-22—**Anesthesiology Review Course.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

CARDIOLOGY

May 26-28—**2nd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

May 30—**Regression of Coronary Artery Disease.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

July 26-August 1—**Current Concepts in Cardiology.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 19 hrs. Contact: UCD.

August 13-15—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $325-$425. Contact: UCSF.

September 12—**Stress Echocardiography.** Sutter Health at Hyatt Regency, Sacramento. Sat. Contact: Sutter Health, (916) 733-3883.

September 25—**Primary Care Issues in Cardiovascular Disease.** Alta Bates Medical Center at Medical Center Auditorium. Fri. 7 hrs. $75. Contact: Mary Grim, (510) 204-1420.

September 25-26—**Coronary Interventions: 1992.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sat. 14 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 1-3—**Cardiology Update—1992.** UCSF at Quail Lodge, Carmel. Thurs-Sat. 11 hrs. $445. Contact: UCSF.

DERMATOLOGY

May 16-17—**Advanced Dermatologic Surgery Workshop.** UCLA at Dermatologic Surgery Center. Sat-Sun. 15 hrs. $400-$800. Contact: UCLA Extension.

July 14-18—**Dr. Hugh Greenway's Eighth Annual Conference: Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation at UCSD Campus and Scripps Clinic, La Jolla. Wed-Sat. 36 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

July 30-August 1—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 24 hrs. $425. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

August 10-12—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 17-18—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Sat-Sun. Contact: UCSF.

EMERGENCY MEDICINE

May 31-June 3—**21st Annual Scientific Assembly.** CAL/ACEP at Westin Mission Hills Resort, Rancho Mirage. Sun-Wed. 13.5 hrs. Contact: CAL/ACEP, (800) 735-2237.

June 22-26—**Emergency Medicine Symposia III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. Contact: UCSD.

August 17-21—**Emergency Medicine Symposia II.** UCSD at Basic Science Building. Mon-Fri. Contact: UCSD.

August 19-23—**Wilderness Medicine: 1992.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $395. Contact: Gene Allred, MD, PO Box 321, Yreka 96097. (800) 888-5632.

October 10—**Emergency Medicine.** Sutter Health at Sheraton Sunrise, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

October 19-23—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

October 26-30—**21st Annual Topics in Emergency Medicine.** UCSF at Ritz-Carlton, San Francisco. Mon-Fri. 32 hrs. $560. Contact: UCSF.

October 29-November 1—**14th Year Biannual Wound Management Workshop.** UCSD at La Jolla Marriott. Thurs-Sun. 18 hrs. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

FAMILY PRACTICE/PRIMARY CARE

May 26-30—**Family Practice Refresher Course.** UCLA-Santa Monica Hospital Medical Center at Miramar Sheraton Hotel, Santa Monica. Tues-Sat. 32 hrs. $445. Contact: UCLA Extension.

June 3—**Primary Care AIDS Update 1992—Maximizing Quality and Length of Life.** Alta Bates Medical Center at Medical Center Auditorium. Wed. 7 hrs. $120. Contact: Mary Grim, (510) 204-1420.

June 15-20—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Marriott Hotel, Newport Beach. Mon-Sat. Contact: UCI.

June 18-21—**Office Gynecology: Primer for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 18 hrs. $188-$325. Contact: UCLA Extension.

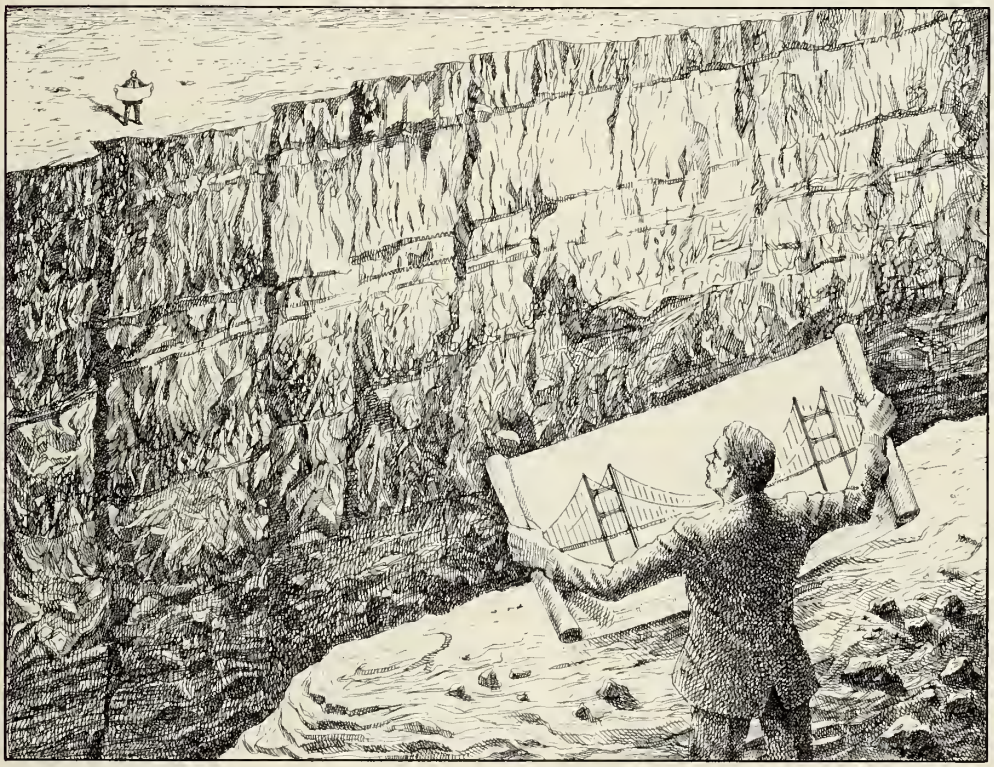
July 6-9—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

July 30-August 2—**Orthopedics for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 20 hrs. $206-$375. Contact: UCLA Extension.

August 7-9—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 476)

We can go a long way toward solving the uninsured problem in California.



But we can't do it alone.

In California, there may be as many as 6,000,000 uninsured people.

Right now, their medical costs are being paid by others. Taxpayers. Medical providers. Insurance companies. And people who can afford health insurance, who are paying more to subsidize those who cannot.

The problem is serious.

Some suggest the only solution is massive government intervention, with all that it entails.

We believe that there are better solutions that will provide high quality care to more people.

The key is extending the private health insurance system to cover all the working people of California and their dependents.

This group accounts for fully 87% of the uninsured.

At Blue Cross, we have developed several innovative solutions for this group. For example, our Small Group Access Program has allowed us to insure over 200,000 employees of small businesses and their dependents.

And, we're happy to say, this initiative is making Blue Cross protection available to small medical groups.

We also have programs to cover part-time employees and people who are temporarily without insurance.

And, further, we support state insurance reforms that will open up the marketplace and provide coverage more broadly.

But Blue Cross can't do it all alone. It takes every insurance company in California to support and participate in similar programs.

Which will make insurance more accessible while helping control the rising cost of health care.

And that should solve a lot of problems. For everyone.

Blue Cross of California

WE MAKE THE SYSTEM WORK FOR YOU.℠

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(Continued from Page 474)

August 21-23—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 21-23—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Loews Coronado Bay Resort, Coronado Island, San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 23-25—**7th Annual Primary Care Medicine: Principles and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 15 hrs. $485. Contact: UCSF.

GERIATRICS

May-June 1992—**Health Aspects of Aging: Promoting Health and Preventing Disability.** UCLA at School of Public Health. Tuesdays. $225. Contact: UCLA.

INFECTIOUS DISEASES

September 19—**AIDS.** Sutter Health at Sacramento Inn. Sat. Contact: Sutter Health, (916) 733-3883.

INTERNAL MEDICINE

May 23-25—**California Society of Internal Medicine—Annual Meeting.** Hotel Del Coronado, San Diego. Contact: Cynthia Eaton, CSIM, (415) 882-5198.

June 22-26—**20th Annual Advances in Internal Medicine.** UCSF at Cole Hall Parnassus Campus. Mon-Fri. 32 hrs. $610. Contact: UCSF.

August 23-28—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. 25 hrs. $480. Contact: UCD.

August 29-September 3—**10th Comprehensive Nephrology Review Course.** UCLA at Beverly Hilton Hotel, Beverly Hills. Sat-Thurs. 51 hrs. $850. Contact: UCLA Extension.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

NEUROLOGY

July 30-August 1—**New Advances in Common Neurological Disorders.** UCSD at Catamaran Hotel, San Diego. Thurs-Sat. Contact: UCSD.

October 23-24—**Transcranial Doppler and Cerebral Blood Flow Monitoring: Applications in Neurology, Neurosurgery and Anesthesiology.** UCLA at Sheraton Miramar Hotel, Santa Monica. Fri-Sat. Contact: UCLA Division of Neurosurgery, (310) 206-0626.

OB/GYN

June 5-7—**Advanced Fetal Heart Rate Monitoring.** Memorial/UCI Center for Health Education at Radisson Hotel, Palm Springs. Fri-Sun. Contact: UCI.

July 26-29—**5th Annual In Vitro Fertilization and Embryo Transfer: A Comprehensive Update—1992.** UCLA at Four Seasons Biltmore Hotel, Santa Barbara. Sun-Wed. 20.5 hrs. $400-$522. Contact: UCLA Extension.

July 29—**10th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Wed-Sat. Contact: UCI.

OCCUPATIONAL/ENVIRONMENTAL

June 4-5—**11th Annual Occupational and Enviromental Medicine Symposium.** UCD at Sacramento Community Convention Center. Thurs-Fri. 18 hrs. $145. Contact: UCD.

July 26-31—**Sports Medicine.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

October 19-30—**Occupational and Environmental Medicine: Session II.** UCSF at Miyako Hotel, San Francisco. 1½ wks. 80 hrs. $1,400. Contact: UCSF.

ONCOLOGY

October 12-18—**18th Annual Lukes Lymphoma Conference.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Sun. 25 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-6310.

October 24—**Melanoma and Pigmented Lesions.** Stanford University Medical Center at Fairchild Auditorium, Stanford. Sat. Contact: STAN.

OPHTHALMOLOGY

May 15-16—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 403C, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 29-August 2—**Summer Institute.** American Academy of Ophthalmology at Sheraton Palace Hotel, San Francisco. Wed-Sun. $325-$500. Contact: Sarah Samuels, (415) 561-8515.

September 10-13—**Uveitis and Retinal Frontiers.** UCSF at Carmel Valley Ranch Resort. Thurs-Sun. Contact: UCSF.

ORTHOPEDICS

June 14-19—**16th Annual Fingers to the Toes.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 28 hrs. $510. Contact: UCD.

October 31—**Orthopedics Symposium.** Sutter Health at Sheraton Sunrise, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

PATHOLOGY

May 1992—**Bay Area Seminars in Cytopathology: 1992.** UCSF at Health Sciences West on Campus. Thursdays. 10 hrs. $150. Contact: UCSF.

May 16—**Fine Needle Aspiration Basic Tutorial.** UCSF. Sat. 12 hrs. $650. Contact: UCSF.

May 21-22—**Curent Issues in Anatomic Pathology: 1992.** UCSF at Holiday Inn Union Square, San Francisco. Thurs-Fri. 13 hrs. $325. Contact: UCSF.

June 6—**Pathology Course.** Sutter Health at Buhler Building, Sacramento. Sat. Contact: Sutter Health, (916) 733-3883.

August 7-8—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD at La Jolla. Fri-Sat. 15 hrs. Contact: Daniel Gormley, MD, 412 W Carroll Dr, Ste 207, Glendora 91740. (818) 963-7684.

(Continued on Page 484)

LET ME TELL YOU ABOUT THE FIRST TIME I WAS ON TELEVISION.

As a family practice physician, Dr. Alvin Sockolov had assisted in operating room number 7 at Sutter General Hospital many times. But after re-injuring his knee, there he was, undergoing ACL surgery at the hands of Dr. David Coward. While choosing surgery was a difficult decision, choosing Sutter General was not. "Dr. Coward prefers to operate at Sutter General," says Dr. Sockolov. "A surgeon needs special equipment, fine instruments, and a capable staff to feel comfortable. Sutter General has what physicians need for procedures to run smoothly." More orthopedic surgeries are performed at Sutter General Hospital than at any other hospital in the region. Advanced diagnostic equipment, specially trained orthopedic nurses, and a team of rehabilitation specialists all help give Sutter General a reputation that's unmatched in Northern California. In addition, educational programs, a health library, outpatient and extended care facilities provide both physicians and patients with the best resources available. "The only problem I had with Sutter General," says Dr. Sockolov, "was that when it came time to leave, I didn't want to go. Everything was top-notch." For more information about available services, call Sutter Orthopedic Center at Sutter General Hospital in Sacramento, (916) 733-8880.

Alvin Sockolov, M.D.

Sutter Orthopedic Center
SUTTER GENERAL HOSPITAL

ABSTRACTS MAY 1992

(Buchwald D, Panwala S, Hooton TM: Use of traditional health practices by Southeast Asian refugees in a primary care clinic. West J Med 1992 May; 156:507-511)

To determine the prevalence of use of traditional health practices among different ethnic groups of Southeast Asian refugees after their arrival in the United States, we conducted a convenience sample of 80 Cambodian, Lao, Mien, and ethnic Chinese patients (20 each) attending the University of Washington Refugee Clinic for a new or follow-up visit. Interpreters administered a questionnaire that dealt with demographics, medical complaints, traditional health practices, health beliefs, and attitudes toward Western practitioners. In all, 46 (58%) patients had used one or more traditional health practices, but the prevalence varied by ethnic group. Coining and massage were used by all groups except the Mien, whereas moxibustion and healing ceremonies were performed almost exclusively by the Mien. Traditional health practices were used for a variety of symptoms and, in 78% of reported uses, patients reported alleviation of symptoms.

The use of traditional health practices is common among Southeast Asian refugees. Clinicians who care for this population should be aware of these practices because they may supersede treatments prescribed by physicians or leave cutaneous stigmata that may be confused with disease or physical abuse. Good patient care may necessitate the use or tolerance of both Western and traditional modalities in many Southeast Asian refugees.

SOUTHEAST ASIAN REFUGEES
NONTRADITIONAL HEALTH PRACTICES
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MIEN
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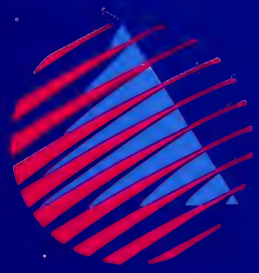
SOUTHEAST ASIAN REFUGEES
NONTRADITIONAL HEALTH PRACTICES
CAMBODIAN
LAO
MIEN
ETHNIC CHINESE

Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

What Is A Single-handed Approach To Blood Pressure Reduction



In Many Patients:

One Agent

Once-A-Day*

One Price

One price for all tablet strengths... 10 mg, 20 mg, 40 mg.

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

Accupril is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

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ONCE-A-DAY*

ACCUPRIL®

quinapril HCl tablets 10, 20, 40 mg

A Single-handed Approach To Blood Pressure Reduction

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

Accupril® (Quinapril Hydrochloride Tablets)

Before prescribing, please see full prescribing information. A brief summary follows.

INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be usetul in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see OOSAGE ANO ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal morbidity and mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation.

Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be pertormed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maximum daily human dose when based on mg/kg and mg/m², respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in gestation and during lactation, reduced offspring body weight was seen at ≥25 mg/kg/day, and changes in renal histology (juxtaglomerular cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Oosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should afways include assessment of renal function (see OOSAGE ANO ADMINISTRATION).

Hyperkafemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use ot potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkafemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Accupril® (Quinapril Hydrochloride Tablets)

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended eff

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation ot therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diu the starting dose of quinapril should be reduced (see OOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase s potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycfine and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPR reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving conc tant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPF
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were adminis concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose w based on a mg/m² basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesent lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Am terial assay with or without metabolic activation. Quinaprl was also negative in the following genetic toxicology studies *vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with m *vitro chromosome* aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. Th were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximu human dose when based on mg/kg and mg/m², respectively).

Pregnancy

Pregnancy Category O: See WARNINGS, Fetal/Neonata morbidity and mortafity.

Nursing Mothers

It is not known if quinapril or its metabolites are secrete human milk. Ouinapril is secreted to a limited extent, ho milk of lactating rats (5% or less of the plasma drug con tion was found in rat milk). Because many drugs are sec human milk, caution should be exercised when ACCUPR given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasr centration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this app relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 5 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

AOVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treate 1 year or more.

Adverse experiences were usually mild and transient.

Oiscontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in plac controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Oizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or unco trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing expenence (t events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascufar: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrova accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinaf: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver funct*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0. 1%). Angioedema associated with edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment wi PRIL should be discontinued and appropriate therapy instituted immediately (See WARNINGS)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blo nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more fr occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often re continued therapy

New! ONCE-A-DAY* ACCUPRIL® quinapril HCl tablets

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

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(Continued from Page 476)

August 9-15—**12th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton, Mauna Lani Kohala Coast, Big Island of Hawaii. Sun-Sat. 27 hrs. $950. Contact: UCSF.

October 10—**Fine Needle Aspiration: Advanced Tutorial XXI.** UCSF. Sat. 12 hrs. $650. Contact: UCSF.

PEDIATRICS

June 26-28—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. Contact: Continuing Education, (619) 576-4072.

July 13-22—**Lactation Management Education Program.** UCSD. 1½ wks. Contact: UCSD.

July 17-August 5—**Lactation Management Education Program.** UCSD. 1½ wks. Contact: UCSD.

August 24-26—**Pediatrics Update: 1992.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

September 21-26 & October 19-24—**Lactation Management Education Program.** UCSD at Wellstart, San Diego. Mon-Sat. Contact: UCSD.

October 19-22—**17th Annual Pediatrics for the Practitioner.** Long Beach Memorial at Mauna Kea Beach Hotel, Kamuela, Hawaii. Contact: Eunice Larson, MD, (310) 595-3422.

PSYCHIATRY

June 5-7—**Treatment of Sexual Problems of Adults Molested as Children.** UCLA at Sunset Village Conference Center. Sat-Sun. 18.5 hrs. $295-$450. Contact: UCLA Extension.

July 24-28—**13th International Congress on Child and Adolescent Psychiatry: Violence and Vulnerability.** UCSF at Fairmont Hotel, Nob Hill, San Francisco. Fri-Tues. Contact: UCSF.

August 4-9—**Neuropsychiatric Aspects of Politics and Politicians.** American Academy of Family Physicians and Southern California Neuropsychiatric Institute at Mauna Kea Beach Hotel, Kamuela. Tues-Sun. 22.5 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

August 7-11—**The Power of the Art—Suggestive Therapeutics: An Introduction to Medical Hypnosis.** UCSD at Mission Bay Hilton, San Diego. Fri-Tues. Contact: UCSD.

PULMONARY MEDICINE

May 16—**Pulmonary Medicine.** Sutter Health at Sheraton Hotel, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

September 17-19—**11th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $410. Contact: UCSF.

RADIOLOGY

May 18-22—**Practical Body Imaging: US, CT, and MRI in the 1990s.** UCSF at Marriott's Tenaya Lodge at Yosemite. Mon-Fri. 21 hrs. $595. Contact: UCSF.

May 21-24—**Doppler and Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Thurs-Sun. 21.5 hrs. Contact: UCSD.

June 4-6—**Interventional Hepatobiliary Radiology: Percutaneous Portacaval Shunts, Biliary Stents, Tumor Chemoembolization, Lithotripsy.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17.5 hrs. $425. Contact: UCSF.

June 4-6—**Vascular Stents 1992: A Comprehensive Symposium.** Scripps Clinic and Research Foundation, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 17-19—**Vascular Imaging and Intervention for the '90s.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Fri-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-22—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Mon-Wed. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-24—**Clinical Imaging for the Non-Radiologist.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Quail Lodge, Carmel. Thurs-Sun. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 27-August 1—**Advanced Neuro MRI—Beyond Spin Echo and Musculoskeletal MRI.** Hoag Memorial Hospital Presbyterian at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Sat. 32 hrs. $645. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 10-14—**Radiology & Clinical Correlation for Non-Radiologists.** UCSD at Hotel Del Coronado, San Diego. Mon-Fri. Contact: UCSD.

September 9-11—**8th Annual Sonography Update.** UCSD at Hotel del Coronado, San Diego. Wed-Fri. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 12-13—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 1-4—**Western Neuroradiological Society Annual Meeting.** Western Neuroradiological Society at Ritz-Carlton, San Francisco. Thurs-Sun. 11.5 hrs. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 24-25—**Musculoskeletal Imaging.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-30—**17th Annual Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 25.25 hrs. $600. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 30-November 1—**12th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

May 1992—**Temporal Bone Surgical Dissection Courses.** House Ear Institute at Los Angeles. 6 days each. 53 hrs. $1100. Contact: Antonio De la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext 7079.

June 25-27—**9th Annual Meeting on Arthroscopic Surgery of the Shoulder.** UCSD and Tri-City Orthopaedic Surgery Medical Group at Hyatt Regency, La Jolla. Thurs-Sat. Contact: James Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 940-2066.

September 14-18—**What's New in Vascular Surgery: A Comprehensive Review and Update.** UCLA at Miramar Sheraton, Santa Monica. Mon-Fri. 34 hrs. $469-$625. Contact: UCLA Extension.

October 31-November 7—**14th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott, Maui, Hawaii. 1 week. Contact: UCLA Extension.

GENERAL/MULTIDISCIPLINARY

June 5-7—**Medicine Meets Virtual Reality.** UCSD at La Jolla Village Inn. Fri-Sun. Contact: UCSD.

July 12-17—**21st Annual Summer School of Alcohol, Tobacco and Other Drugs.** UCSD. Sun-Fri. Contact: UCSD Extension.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 12-13—**Fifth Annual Summer in the Mountains Conference.** Children's Hospital of Denver in Gunnison. Fri-Sat. Contact: Mary Haley, (303) 861-6946 or (800) 225-0010.

June 19-20—**Neonatal Resuscitation Course.** Children's Hospital of Denver in Laramie, Wyoming. Fri-Sat. Contact: Lois Pine, (303) 777-7166.

(Continued on Page 486)

SEMINARS IN

Obstetrics and Gynecology

IN

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"Update in Clinical Obstetrics"

June 13-14, 1992

• SATURDAY, JUNE 13, 1992
7:30 - 8:15 a.m.
"The Human Genome Project; Implications for the Practice of OB" — Dr. Benjamin P. Sachs

8:30 - 9:15
"Early Pregnancy Evaluation" — Dr. Thomas R. Moore

9:30 - 10:15
"Ultrasound Diagnosis of Chromosomal Abnormalities" — Dr. Charles Lockwood

10:30 - 11:15
"What's New In Tocolytics" — Dr. Moore

11:30 - 12:15
"Home Uterine Contraction Monitoring: A Controversial Technology" — Dr. Sachs

• SUNDAY, JUNE 14, 1992
7:30 - 8:15 a.m.
"Fetal Fibronectin" — Dr. Lockwood

8:30 - 9:15
"Clinical Applicability of Doppler Ultrasound" — Dr. Moore

9:30 - 10:15
"Infant Mortality; What Role Does the Obstetrician Play?" — Dr. Sachs

10:30 - 11:15
"Pre-Eclampsia" — Dr. Lockwood

11:30 - 12:15
"Substance Abuse In Pregnancy" — Dr. Ken Lyon Jones

"Office Gynecology"

September 19-20, 1992

• SATURDAY, SEPTEMBER 19, 1992
7:30 - 8:15 a.m.
"Treatment of Symptomatic Vulvar Lesions" — Dr. Leo Twiggs

8:30 - 9:15
"Management of the Menopausal Woman" — Dr. William Spellacy

9:30 - 10:15
"Treating the Abnormal Pap Smear" — Dr. Twiggs

10:30 - 11:15
"Hyperprolactemia and Galactorrhea" — Dr. Spellacy

11:30 - 12:15
"New and Future Methods of HPV Therapy" — Dr. Twiggs

• SUNDAY, SEPTEMBER 20, 1992
7:30 - 8:15 a.m.
"Syphilis, Gonorrhea, and Chlamydia: Old Infections, New Problems" — Dr. David Grimes

8:30 - 9:15
"GNRH - Uses in Gynecology" — Dr. Spellacy

9:30 - 10:15
"RU - 486" — Dr. Grimes

10:30 - 11:15
"Systemic Effects of Oral Contraceptives" — Dr. Spellacy

11:30 - 12:15
"Norplant" — Dr. Grimes

"Perinatal Medicine"

November 14-15, 1992

• SATURDAY, NOVEMBER 14, 1992
7:30 - 8:15 a.m.
"Preconception Counseling" — Dr. Robert Resnik

8:30 - 9:15
"Heart Disease in Pregnancy" — Dr. Stephen Clark

9:30 - 10:15
"Fetal Assessment" — Dr. Jeffrey Lipshitz

10:30 - 11:15
"Antepartum Fetal Surveillance of the Postdated Pregnancy" — Dr. Jeffrey Phelan

11:30 - 12:15
"The Role of Lupus Anticoagulant and Anticardiolipin Antibodies in Reproductive Loss" — Dr. Resnik

• SUNDAY, NOVEMBER 15, 1992
7:30 - 8:15 a.m.
"Terbutaline Pump Therapy" — Dr. Phelan

8:30 - 9:15
"Managing Complications of Severe Pregnancy Induced Hypertension" — Dr. Clark

9:30 - 10:15
"The Evaluation and Management of the Patient with Intrauterine Growth Retardation" — Dr. Resnik

10:30 - 11:15
"Role of Amnioinfusion" — Dr. Phelan

11:30 - 12:15
"Management of the Post-Partum Hemorrhage" — Dr. Clark

"Reproductive Endocrinology"

February 6-7, 1993

• SATURDAY, FEBRUARY 6, 1993

7:30 - 8:15 a.m.
"The Future of GYN" — Dr. Alan DeCherney

8:30 - 9:15
"Pathophysiology of Adhesion Formation and Treatment at Pelviscopy" — Dr. Michael Diamond

9:30 - 10:15
"RU - 486" — Dr. DeCherney

10:30 - 11:15
"Intrauterine Insemination" — Dr. Andrew Friedman

11:30 - 12:15
"Endocrine Aspects of Menopause" — Dr. DeCherney

• SUNDAY, FEBRUARY 7, 1993
7:30 - 8:15 a.m.
"Modern Diagnosis of Ectopic Pregnancy" — Dr. Bruce Shapiro

8:30 - 9:15
"Surgical Treatment of Ectopic Pregnancy" — Dr. Diamond

9:30 - 10:15
"Distal Tubal Disease; IVF vs. Surgery" — Dr. Friedman

10:30 - 11:15
"GNRH Use in Management of Uterine Myomata and Endometriosis" — Dr. Friedman

11:30 - 12:15
"Hysteroscopic Treatment of Intrauterine Lesions" — Dr. Diamond

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(Continued from Page 484)

June 23-25—**Community Health Traineeship.** Children's Hospital, Denver. Tues-Thurs. Contact: Pat Winter, (303) 861-6668.

July 9—**Cultural Considerations in Perinatal Nursing.** Children's Hospital at University Hospital, Denver. Thurs. Contact: Trish Beachy, (303) 270-8376.

August 17-21—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

September 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

September 16-17—**Neonatal Resuscitation Hospital-Based Instructor Course.** Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

September 17, 24, October 1, 8—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Four consecutive Thursdays. Contact: Trish Beachy, (303) 270-8376.

October 23-24—**Fifteenth Annual Perinatal Conference.** Children's Hospital of Denver in Fort Collins. Fri-Sat. Contact: Sharon Adams, (303) 861-6946 or (800) 225-0010.

November 19-22—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

November 30-December 4—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

IDAHO

July 30-August 1—**Idaho Medical Association—Annual Meeting.** Coeur d'Alene. Thurs-Sat. Contact: Idaho Medical Assn, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 14-15—**6th Annual Multicultural Mental Health Conference on Family and Children.** Hilton Hotel, Albuquerque. Thurs-Fri. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

May 15-16—**New Mexico Medical Society Annual Meeting.** The Marshall Building, Albuquerque. Fri-Sat. Contact: Glenn Taylor, New Mexico Medical Society, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

May 28-29—**3rd Annual Southwest Wound Care Symposium.** Holiday Inn-Pyramid, Albuquerque. Thurs-Fri. Contact: Diane Atchinson, PO Box 22569, Kansas City, MO 64113-0569. (816) 765-6644 or (800) 245-0372.

July 13-17—**Imaging 1992: Ultrasound, CT, MR, and Mammography.** Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 7-11—**Mammography Update.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

June 21-27—**School on Alcoholism, Drug Dependencies** (Sponsor: UUSM). Sun-Sat. U of U Browning Auditorium. Contact: UUSM.

June 24-27—**Slice of Life: Interactive Video and Related Multimedia Technology in Health Education** (Sponsor: UUSM). Wed-Sat. U of U Eccles Genetics Auditorium. Contact: UUSM.

July 12-17—**Update in Internal Medicine Focus on Ambulatory Care Medicine** (Sponsor: UUSM). Sun-Fri. Snowbird. Contact: UUSM.

July 31-August 1—**UOS Shakespearean Festival Meeting** (Sponsor: UOS). Fri-Sat. Contact UOS.

August 6-8—**ISLD Dental Congress** (Sponsor: UUSM). Tues-Sat. Marriott Hotel, Salt Lake City. Contact: UUSM.

September 10—**Monthly Meeting** (Sponsor: UOS). Thursday evening. Contact: UOS.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.
WRI:	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

(Continued on Page 487)

(Continued from Page 486)

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 15-16—**Medical and Orthopedic Issues of Active and Athletic Women.** Seattle. Fri-Sat. Contact: VMMC.

May 16—**Infectious Disease in Primary Care.** Seattle. Sat. Contact: U/W.

May 21-22—**Cardiology Conference.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

May 22-23—**Medicine Update.** Seattle. Fri-Sat. Contact: U/W.

May 27—**Pesticide Medicine.** Eastern Washington. Wed. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 28-30—**Musculoskeletal Disease.** Seattle. Thurs-Sat. Contact: U/W.

May 29-30—**Spinal Cord Injury.** Seattle. Fri-Sat. Contact: U/W.

May 30—**The Fetal Patient.** Seattle. Sat. Contact: VMMC.

June 11—**Endocrinology.** Everett. Thurs. Contact: PNMEI, (206) 258-6322.

June 12-13—**Urology.** Seattle. Fri-Sat. Contact: U/W.

June 18-20—**Diabetes Update.** Seattle. Thurs-Sat. Contact: U/W.

June 22-23—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: PCMS.

June 25-27—**Refocus on Women's Health Care.** Seattle. Thurs-Sat. Contact: U/W.

June 26—**Sports Medicine.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

July 23-26—**Current & Emerging Issues in Cancer Pain.** Seattle. Thurs-Sun. Contact: U/W.

July 29-31—**STD Update.** Seattle. Wed-Fri. Contact: U/W.

July 30-August 1—**STD Update.** Seattle. Wed-Fri. Contact: U/W.

August 3-8—**Summer Seminar in Medical Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 21-22—**Regional CME Network Meeting.** Seaside, Oregon. Fri-Sat.

September 14-18—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

September 23-24—**Critical Care.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

October 1-4—**Washington State Medical Association Annual Meeting.** Yakima. Thurs-Sun. Contact: WSMA.

October 15-17—**Endoscopic Sinus Surgery.** Seattle. Thurs-Sat. Contact: U/W.

October 22—**General Surgery Review.** Everett. Thurs. Contact: PNMEI, (206) 258-6322.

October 23—**Perinatology.** Fri. Tacoma. Contact: Multicare, (206) 594-1221.

November 12—**Dermatology.** Thurs. Everett. Contact: PNMEI, (206) 258-6322.

November 12-13—**Advances in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 20—**Orthopaedic Trauma Update.** Spokane. Fri. Contact: U/W.

December 4-5—**Urology Annual Meeting.** Vancouver, BC. Fri-Sat. Contact: NWUS, (206) 441-9762.

December 10-12—**8th Infectious Disease Conference.** Thurs-Sat. Everett. Contact: PNMEI, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 11-13—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

August 24-26—**Eighteenth Annual Tutorials in the Tetons.** Jackson Lake Lodge, Moran. 14.5 hrs. Contact: American College of Cardiology, (800) 257-4739. ◆

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In Memoriam

California Medical Association

Banakas, Leon T., Saratoga. Died Feb 14, 1992. Graduate of University of Tennessee, Memphis, 1958. Licensed in California in 1963. Dr Banakas was a member of the Santa Clara County Medical Association.

Berroll, Sheldon, San Francisco. Died Dec 31, 1991, aged 61. Graduate of University of California, Irvine, 1962. Licensed in California in 1962. Dr Berroll was a member of the San Francisco Medical Society.

Bien, Charles W., Vallejo. Died Feb 13, 1992, aged 87. Graduate of Peking Union Medical College, Peking, China, 1930. Dr Bien was a member of the Solano County Medical Society.

Binger, Grace Gunn, Santa Clara. Died Feb 4, 1992, aged 83. Graduate of University of California, 1939. Licensed in California in 1939. Dr Binger was a member of the Santa Clara County Medical Association.

Conant, Robert F., Grass Valley. Died Feb 13, 1992, aged 74. Graduate of University of Minnesota, 1941. Licensed in California in 1946. Dr Conant was a member of the Placer-Nevada County Medical Society.

Cosand, Merle, San Bernardino. Died Dec 20, 1991, aged 84. Graduate of Northwestern University Medical School, Chicago, Illinois, 1935. Licensed in California in 1936. Dr Cosand was a member of the San Bernardino County Medical Society.

Cullen, James, San Francisco. Died Jan 12, 1992, aged 42. Graduate of University of Michigan, Ann Arbor, 1975. Licensed in California in 1975. Dr Cullen was a member of the San Francisco Medical Society.

Fast, John G., Riverside. Died Jan 29, 1992, aged 75. Graduate of University of Minnesota, 1942. Licensed in California in 1942. Dr Fast was a member of the Riverside County Medical Association.

Fink, Aaron, Mountain View. Died Feb 1, 1992, aged 66. Graduate of University of Illinois, Chicago, 1954. Licensed in California in 1954. Dr Fink was a member of the Santa Clara County Medical Association.

Goulding, Robert L., Watsonville. Died Feb 13, 1992, aged 74. Graduate of University of Cincinnati, Ohio, 1944. Dr Goulding was a member of the Santa Cruz County Medical Society.

Greengard, Milton, Oakland. Died Jan 26, 1992, aged 86. Graduate of University of Minnesota, 1932. Dr Greengard was a member of the Alameda-Contra Costa Medical Association.

Guttentag, Otto, San Francisco. Died Jan 13, 1992, aged 91. Graduate of Martin Luther University, 1925. Licensed in California in 1929. Dr Guttentag was a member of the San Francisco Medical Society.

Hack, Raymond L., Salinas. Died Jan 21, 1992, aged 75. Graduate of University of Oregon Medical School, Portland, 1943. Dr Hack was a member of the Monterey County Medical Society.

Harden, Bernard L., Berkeley. Died Oct 9, 1991, aged 71. Graduate of University of Kansas, Kansas City, 1946. Dr Harden was a member of the Alameda-Contra Costa Medical Association.

Hinahon, Jaime, El Cajon. Died Feb 5, 1992, aged 33. Graduate of University of Santo Tomas, 1982. Dr Hinahon was a member of the San Diego County Medical Society.

Jesberg, Norman, Los Angeles. Died Jan 6, 1992, aged 74. Graduate of University of Southern California, Los Angeles, 1944. Licensed in California in 1944. Dr Jesberg was a member of the Los Angeles County Medical Association.

Juul, Clement O., Oakland. Died Dec 17, 1991, aged 80. Graduate of St Louis University, Missouri, 1944. Dr Juul was a member of the Alameda-Contra Costa Medical Association.

Katz, Lawrence Roy, Chico. Died Jan 14, 1992, aged 41. Graduate of University of Pennsylvania, Philadelphia, 1981. Dr Katz was a member of the Butte-Glenn Medical Society.

Malone, Robert F., Mountain View. Died Dec 4, 1991, aged 70. Graduate of University of Colorado, Denver, 1947. Licensed in California in 1949. Dr Malone was a member of the Santa Clara County Medical Association.

Mathiasen, Henning W., Sacramento. Died Jan 24, 1992, aged 83. Graduate of Creighton University, Omaha, Nebraska, 1932. Licensed in California in 1962. Dr Mathiasen was a member of the Sacramento-El Dorado Medical Society.

Moore, Lawrence T., San Diego. Died Jan 17, 1992, aged 68. Graduate of Harvard Medical School, Boston, Massachusetts, 1950. Dr Moore was a member of the San Diego County Medical Society.

Nadridge, Maurice S., Palm Springs. Died Nov 9, 1991, aged 67. Graduate of University of California, Irvine, 1958. Dr Nadridge was a member of the Orange County Medical Association.

Rubrecht, William K., Monterey. Died Jan 21, 1992, aged 68. Graduate of University of California, Los Angeles, 1956. Dr Rubrecht was a member of the Monterey County Medical Society.

Schwartz, Irving, San Francisco. Died Jan 28, 1992, aged 83. Graduate of Stanford University School of Medicine, Stanford, California, 1935. Licensed in California in 1935. Dr Schwartz was a member of the San Francisco Medical Society.

Smith, Daniel D., Watsonville. Died Feb 10, 1992, aged 86. Graduate of University of Nebraska, Omaha, 1934. Dr Smith was a member of the Santa Cruz County Medical Society.

Spencer, Le Grand D., Anaheim. Died Dec 29, 1991, aged 81. Graduate of St Louis University, Missouri, 1942. Dr Spencer was a member of the Orange County Medical Association.

Stenzel, David M., San Diego. Died Jan 17, 1992, aged 63. Graduate of University of Minnesota, 1954. Dr Stenzel was a member of the San Diego County Medical Society.

Yelsa, Charles J., Colton. Died Jan 18, 1992, aged 63. Graduate of California College of Medicine, Irvine, 1959. Licensed in California in 1959. Dr Yelsa was a member of the San Bernardino County Medical Society.

Denver Medical Society

Apling, Mark L. Died Dec 21, 1991, aged 43. Graduate of Ohio State University College of Medicine, Columbus, 1973. Licensed in Colorado in 1987.

Idaho Medical Association

Cochrane, Allen M., Lewiston. Died Jan 1991, aged 81. Graduate of Rush Medical College, Chicago, Illinois, 1942. Licensed in Idaho in 1965. Dr Cochrane was a member of the North Idaho District Medical Society.

Rigby, Clifford B., Rigby. Died Feb 8, 1992, aged 83. Graduate of George Washington University, Washington, DC, 1938. Licensed in Idaho in 1938. Dr Rigby was a member of the Upper Snake River Medical Society.

Ross, Warren B., Nampa. Died Feb 1, 1992, aged 80. Graduate of University of Iowa, Iowa City, 1935. Licensed in Idaho in 1937. Dr Ross was a member of the Southwestern Idaho District Medical Society.

New Mexico Medical Society

Pitcher, Loren, Albuquerque. Died Feb 3 1992, aged 60. Graduate of Northwestern University School of Medicine, Chicago, Illinois 1958. Licensed in New Mexico in 1978. D Pitcher was a member of the Greater Albuquerque Medical Association.

FREE HIV RISK ASSESSMENT PROGRAM AVAILABLE

CMA's Department of Physician Education has produced a new CME program, "HIV Risk Assessment: Methods and Guidelines," which is available free to physicians. This program teaches effective strategies developed by expert physicians to identify patients who are potentially at risk for HIV infection. Worth one hour of CME Category I credit, the program is designed for groups of 5-20 physicians.

The program features CMA's award-winning, 11-minute video, "Let's Talk," which highlights several methods physicians can use to perform HIV assessment with patients. Participants receive a course outline, camera-ready slide reproductions, a compilation of state laws pertaining to HIV/AIDS, community resource guide to HIV testing and counseling, risk assessment guidelines, and a model HIV consent form and patient information pamphlet.

Those interested in taking part in this unique CME program should contact Amy Wright in CMA's Department of Physician Education at 415/882-5186.

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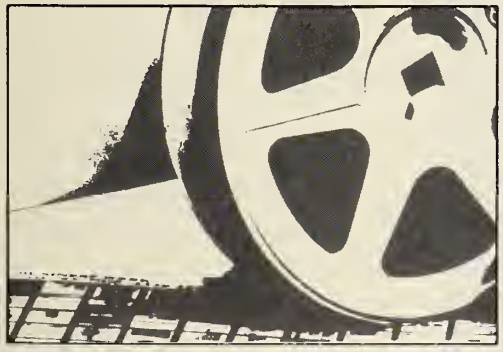

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BuSpar® (buspirone HCl)

References: 1. Data on file, Bristol-Myers Squibb Company **2.** Cohn JB, Bowden CL, Fisher JG, Rodos JJ. Double-blind comparison of buspirone and clorazepate in anxious outpatients with or without depressive symptoms *Psychopathology.* 1992;25:10-21. **3.** Feighner JP, Cohn JB. Analysis of individual symptoms in generalized anxiety—a pooled, multistudy, double-blind evaluation of buspirone *Neuropsychobiology.* 1989;21:124-130 **4.** Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med.* 1987;82(suppl 5A):20-26. **5.** Newton RE, Marunycz JD, Alderdice MT, Napoliello MJ. Review of the side-effect profile of buspirone *Am J Med.* 1986;80(suppl 3B):17-21.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General*** – *Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (*eg*, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (*ie*, represent akathisia).

Information for Patients – Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions – Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations of SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility – No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects – Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers – Administration to nursing women should be avoided if clinically possible.

Pediatric Use – The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly – No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function – Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed*** – The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment – The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials – Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation – The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular* – frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System* – frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT* – frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine* – rare: galactorrhea, thyroid abnormality. *Gastrointestinal* – infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary* – infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal* – infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological* – infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory* – infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function* – infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin* – infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory* – infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous* – infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience – Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: ***Controlled Substance Class*** – Not a controlled substance.

Physical and Psychological Dependence – Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (*eg*, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms*** – At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdosage Treatment – General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

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Please see references and brief summary on adjacent page.

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Articles

Phenotype Recognition
Clinicians' Contributions to Molecular Genetics

KENNETH D. GARDNER, Jr, MD, *Albuquerque, New Mexico*

Medullary cystic disease, Alport's syndrome, and autosomal dominant polycystic kidney disease are inherited renal disorders whose genetic bases are better understood because of careful clinical observation. I explore the relationships among some clinical aspects of each of these conditions, the rapidly advancing field of molecular genetics, and the ethical issues that need to be addressed before gene identification becomes too widely applied as a diagnostic tool.

(Gardner KD: Phenotype recognition—Clinicians' contributions to molecular genetics. West J Med 1992 May; 156:491-494)

The advent of techniques for gene location and identification has propelled hereditary disease toward the forefront of clinical medicine. Practitioners, long frustrated by an inability to provide anything but supportive therapy, now may anticipate opportunities for improved diagnosis and care when dealing with familial disease.

Nephrology is in the vanguard of specialties affected by advances in molecular genetics. Three inherited renal diseases deserve the attention of all clinicians: medullary cystic disease, Alport's syndrome, and autosomal dominant polycystic kidney disease. These conditions are among the most prevalent of all inherited disorders. They, especially the last, contribute substantially to morbidity, affecting hundreds of thousands of people worldwide, and to health care costs, obligating annual expenditures in the hundreds of millions of dollars in the United States alone. The patterns of inheritance of these diseases are now better understood because practitioners were careful earlier to delineate their distinguishing clinical features. Furthermore, these conditions illustrate the credits and debits that derive from applying molecular biology to clinical medicine. They are examples of the symbiotic relationship that must exist between practitioner and molecular geneticist if the search for any mutated gene is to succeed.

As a discipline molecular genetics is rapidly expanding the number of diagnostic tests whose clinical application and interpretation will rest with providers of health care, not with laboratory scientists. Clinicians need to know of these tests and to understand their limitations. They also need to appreciate the necessity of recognizing familial disease and how important it can be to document subtle and seemingly unimportant differences in initial manifestations among affected persons.

Molecular geneticists rely on clinicians to discern and describe phenotypes. The three heritable renal diseases reviewed are genetically heterogeneous: multiple gene effects appear to be responsible for the phenotypic expression that characterizes each disorder. Medullary cystic disease exemplifies the way in which answers to one question in the family history evolve to suggest that multiple gene effects are present. Alport's syndrome illustrates how such clinical observation has led molecular geneticists to the identification of mutated genes. Autosomal dominant polycystic kidney disease demonstrates some of the complexities that may arise when phenotypic identification is imperfect.

Medullary Cystic Disease

From the 1940s to the 1960s, a number of reports documented the cases of children and young adults who had died of renal failure of unknown cause with scarred and shrunken kidneys at autopsy. Some kidneys contained cysts in the corticomedullary and medullary regions; others did not. The disorder was recognized as a distinct entity known as medullary cystic disease (MCD) in the United States and nephronophthisis in Europe.[1]

In some kindreds, cases of MCD were sporadic,[2] whereas in others in which siblings were affected, MCD appeared to be familial, but the issue of heritability was unsettled.[3] In the mid-1960s, I encountered two families in which MCD affected members in sequential generations, a pattern of inheritance consistent with that of a dominant trait.[4] The disorder appeared in roughly half the offspring of an affected parent and did so over three or more generations.

When kidneys from members of these families were examined, no differences in morphology could be detected. Significant differences were found in ages at death, ranging from the first to the fifth decades. Half of the deaths occurred during the third decade of life (Figure 1). When attention was

Figure 1.—Ages at death of 28 persons with medullary cystic disease are shown in the histogram (adapted from Gardner[4]). A bell-shaped distribution is present, with the greatest number of deaths occurring between 20 and 24 years of age.

From the Department of Medicine, University of New Mexico School of Medicine, Albuquerque.
Reprint requests to Kenneth D. Gardner, Jr, MD, Box 535, Graduate Medical Education, University of New Mexico School of Medicine, Albuquerque, NM 87131.

ABBREVIATIONS USED IN TEXT

ADPKD = autosomal dominant polycystic kidney disease
MCD = medullary cystic disease

paid to the number of generations within families in which MCD appeared—one versus more than one generation—an informative pattern was found (Figure 2). When only siblings were affected, deaths occurred at younger ages than when successive generations were affected. These data support the concept that MCD is familial and can be inherited as either a recessive or a dominant trait.[1] With dominantly transmitted disease (Figure 3), a significant difference was found between members of the two prototype families. Deaths from MCD in one family peaked between the ages of 20 and 24 years, in contrast to the second family, which had a peak in the fourth decade.[4]

Geneticists recognize such differences in ages at death as presumptive evidence that different gene effects operate in an inherited disorder. It now is thought that more than one gene is responsible for MCD.

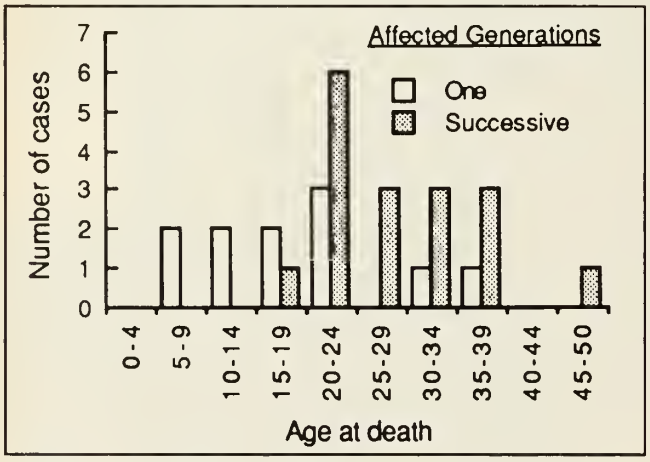

Figure 2.—Ages at death from medullary cystic disease of the same 28 persons shown in Figure 1 are distributed according to generations affected. Of 11 cases from families in which the disease was restricted to a single generation, the median age at death was younger than 20 years. Of 17 cases from families in which the disease affected persons in three or more successive generations, the median age at death was older than 25 years. The difference is statistically significant ($P < .05$; Student's t test).

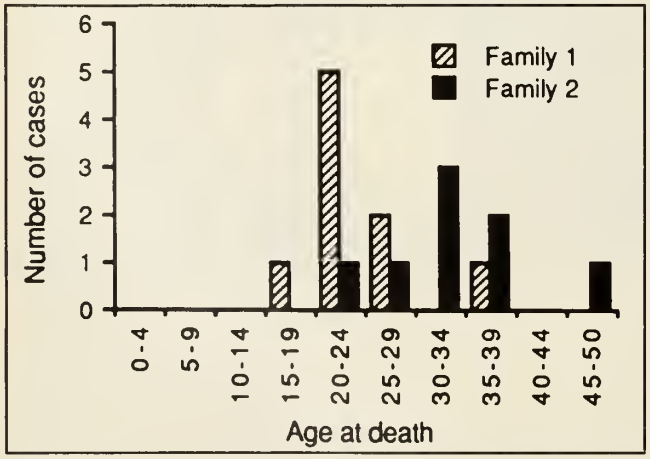

Figure 3.—Ages at death are shown in members of two families in which medullary cystic disease affected persons in two or more successive generations (the same cases shown in the stippled bars of Figure 2). The mean age at death was 22 years in family 1 and 32 years in family 2. The difference ($P < .015$) is statistically significant (Student's t test) (adapted from Gardner[1,4]).

Alport's Syndrome

Alport's syndrome is a rare disease but one of the most common hereditary renal diseases. Affected persons characteristically have progressive renal failure, hematuria, erythrocyte urinary casts, high-tone nerve deafness, and ocular abnormalities. At one time, the method of inheritance was unclear. A defect of an autosomal dominant gene seemed likely, but in a number of families the ratio of affected to unaffected offspring deviated from the expected 1:1 ratio.[5] Furthermore, male patients with Alport's syndrome seemed to die of renal failure more frequently and at younger ages than did affected female patients.

Inheritance patterns were subsequently clarified by the data presented in modified form in Figure 4.[5] It was noted

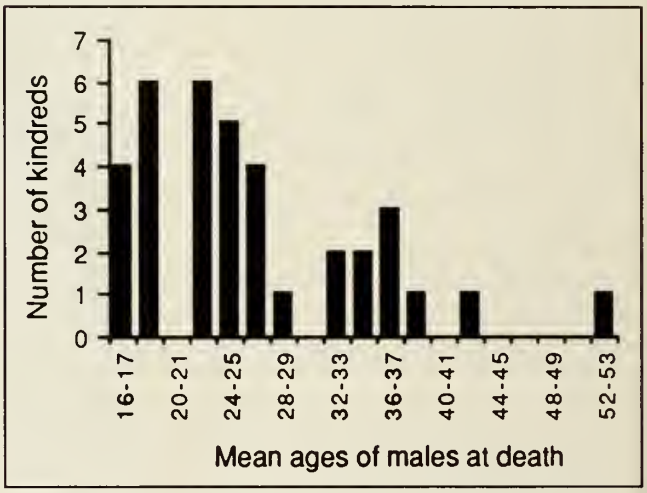

Figure 4.—Mean ages at death of male members in 36 families with Alport's syndrome are depicted. Two populations are suggested by distribution of the data: families in which male members die before the age of 30 years and families in which male members die after the age of 30 years (adapted from Tishler and Rosner[5]).

that although men in most of these families die before the age of 30, in some families they live for four to seven decades. This pattern of death among men suggested two genetic forms of the disorder: when affected by one form, men died at a younger age than when affected by the second, when they survived to the later decades of life. On histologic examination, splitting of the glomerular basement membrane occurs in a fraction of cases from both groups.[6] As with MCD, light-microscopic changes in the kidneys do not correlate with clinical manifestations or ages at the time of death.

In further searches for affected members, concentrating on patients with chronic hematuria and a family history of chronic glomerulonephritis,[7] clinical geneticists have determined that Alport's syndrome exists primarily in X-linked forms but probably also exists in autosomal dominant and recessive forms.[8] Recently, techniques of chromosomal linkage analysis identified multiple different mutations at the site of a gene responsible for collagen IV production in persons with X-linked Alport's syndrome.[9] Thus, this syndrome is a genetically heterogeneous renal disorder for which several mutated genes have been identified; presumably more will be found. The story is not so clear-cut for polycystic disease,

perhaps because its phenotypic expression has not been defined adequately.

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is a heritable renal disease for which genetic heterogeneity was not suspected until the advent of linkage analyses. Two separate chromosomal locations are probable for the mutated genes that are thought to cause the disorder.

Typically, ADPKD results in enlarging cystic kidneys, progressive azotemia, and death unless renal transplantation or dialysis is done. It affects approximately 500,000 persons in the United States and is more common in the general population than Huntington's disease, sickle cell anemia, or cystic fibrosis. Autosomal dominant polycystic kidney disease accounts for approximately 10% of cases of end-stage renal disease. Until a decade ago, it was considered a monogenic disorder—that is, a one gene:one phenotype disease. Events have proved that concept to be incorrect.

More recently, molecular geneticists have successfully applied a technique called restricted fragment length polymorphism analysis to clarify the genetic basis of ADPKD. This technique makes use of restriction endonucleases, enzymes that recognize specific base pair sequences along DNA molecules, to cut DNA. Pieces of DNA obtained from affected and unaffected members of the same family are compared. Differences in the patterns of the DNA pieces obtained—polymorphisms in the restricted fragment lengths of DNA—are matched to carriers of the disease. Families are compared, consistencies are sought, and results are analyzed statistically to determine the likelihood of given patterns or given pieces of DNA being associated with the disorder being investigated.

In theory, a fragment of DNA that always is found among those with a given phenotype and never in those without this phenotype would contain the suspect gene. Fragments of DNA that frequently, but not always, associate with a phenotype would likely be near the causative gene but might not include it. Base pair sequences in some of these latter fragments can be used as markers of the mutated gene's presumed location.

The ADPKD was the third heritable disorder—after Huntington's disease and Duchenne muscular dystrophy—to have the site of its mutated gene localized to a specific chromosome through the use of this technique, called linkage analysis.[10] In 1985 the short arm of chromosome 16 was identified by these techniques as the probable locus of a mutated gene responsible for ADPKD.[11] At that time it seemed likely that the gene itself soon would be identified and that diagnosis of the disorder before birth or before clinical disease developed would become possible. Even the distant possibility of a cure through gene therapy could be postulated. Commercial tests for ADPKD markers became available.

These early expectations were dashed in 1988. Test kits were withdrawn. Kimberling and co-workers published a compelling demonstration that ADPKD did not link to markers on chromosome 16 in one large family under their observation.[12] The finding meant that in this kindred, a mutated gene at a second chromosomal location must have produced the ADPKD phenotype. In subsequent studies, it has been found that the ADPKD phenotype does not link with markers on chromosome 16 in approximately 5% and 10% of all families. Paralleling the observations in MCD and Alport's syndrome, clinical evidence of the disease appears at significantly different ages, depending on which genotype is involved. Persons carrying the gene that is located off chromosome 16, the *PKD2* gene, do not succumb to renal failure during the sixth decade of life as is described for the *PKD1*-associated disorder. The *PKD2* carriers live into their seventh to ninth decades and often die of nonrenal causes.[13]

The genetics of ADPKD is still unclear. One problem has been summarized as follows: "The discovery that mutations in more than one gene may lead to indistinguishable phenotypes has posed problems for ADPKD diagnosis that is based on linkage analysis."[14]

There is evidence that two renal phenotypes may exist and that all kidneys may not be alike in ADPKD. In polycystic kidneys, cysts are filled with fluids of varied composition.[15,16] For example, the concentration of sodium in cyst fluids ranges from 1 to more than 200 mmol per liter (1 to >200 mEq per liter). Parallel differences in concentrations of the hydrogen ion and other crystalloids led investigators to speculate that cysts arise from different segments of the nephron and that they contain fluids whose compositions are reminiscent of the tubules or ducts from which they arose: high sodium, low potassium, and low hydrogen concentrations in cysts arising from the proximal or permeant segment of the nephron and low sodium, high potassium, and high hydrogen concentrations in cysts arising from the distal nephron.[15] The ultrastructural characteristics of cells that line the two types of cysts are different, supporting the idea that cysts in polycystic kidneys are different and are not simply extremes of a continuum. Instead of all ADPKD kidneys containing an admixture of high- and low-sodium (permeant and impermeant; proximal and distal) cysts, some ADPKD kidneys contain exclusively high-sodium cysts (Figure 5).[16] Although

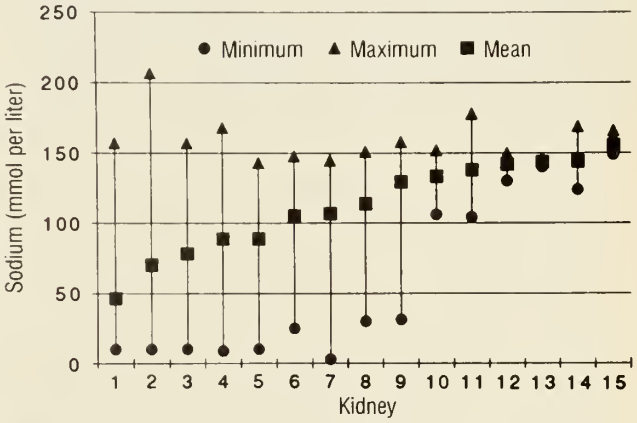

Figure 5.—Mean and range of sodium concentrations are shown for 5 to 25 aspirated cyst fluids from 15 kidneys in persons with autosomal dominant polycystic kidney disease. Fluids from kidneys 1 to 9 had sodium concentrations more than and less than 50 mmol per liter (50 mEq/liter). In contrast, in the cysts of kidneys 10 to 15, all measured sodium concentrations were more than 100 mmol per liter (100 mEq per liter). The likelihood is <.002 that these two groups of kidneys come from a single universe. It is more likely that all kidneys in persons with autosomal dominant polycystic kidney disease are not alike.

other explanations are possible, it is most attractive to speculate that different gene effects are responsible for the two types of kidneys. More cysts, more kidneys, and more families need to be studied.

Ethical Issues

Two themes should be evident from my review. First, clinicians make important contributions when they recognize

the familial nature of a disease and when they detect subtle differences in its initial manifestation among affected family members or between affected families. An observation that a given set of signs or symptoms breeds true within a kindred often is the first indication of a genetic disorder. Such has been the experience with MCD, Alport's syndrome, and ADPKD, disorders whose heritability and genetic heterogeneity were not suspected until implicated by the careful observations of clinicians.

Second, molecular genetics will influence the practice of medicine increasingly in the years ahead. Linkage analysis and gene identification already enable heritable disease to be diagnosed in the prenatal and preclinical stages.[10,17] Linkage analysis, as exemplified by experience with ADPKD, is not infallible, however. Crossovers, the existence of a second gene, and perhaps inadequate definition of the phenotype combine to introduce as much as a 10% potential for error in the diagnosis of ADPKD in one person who is at risk because of a positive family history. Such a degree of error is too high to be clinically acceptable for use in genetic counseling or in deciding fetal survival.[6,18]

The societal consequences of preclinical diagnosis in such diseases as Alport's syndrome, MCD, and ADPKD have not been established.[19] The merits of gene testing have yet to be debated adequately. One can argue that gene testing should be mandatory to ensure proper care or voluntary to protect patient autonomy. One can debate the issues of disclosure versus confidentiality. Once the outcome is known, presuming accuracy, should the results of gene testing on a fetus be used to decide whether or not pregnancy should continue? Should results from testing a person at risk be released to prospective insurers or spouses? What is a physician's responsibility in these settings? The labeling of a person as one who will die or be disabled because of an untreatable heritable disorder could threaten that person's employment, insurance, marriage, or psychic stability to unacceptable degrees.[19] These are important concerns that have no ready solutions. Physicians are well advised to refer patients with questions about when to obtain gene testing and how to interpret results to the few skilled and experienced geneticists who can speak from knowledge and experience.[18,19]

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Cancer Screening in Older Adults

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Adults aged 65 and older represent an increasingly important segment of the US population. Cancer is an important cause of death in this group. Screening for cancer can significantly reduce cancer incidence and mortality. In this review I address screening for breast, cervical, prostate, lung, colorectal, and ovarian cancer in older Americans. Decisions about screening for cancer must consider the effects of screening, diagnostic evaluations, and treatments on the quality of life of each person.

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Screening for the early detection of cancer has been shown to decrease both cancer incidence and cancer mortality and is an important part of primary care practice.[1,2] Most studies on the efficacy of cancer screening, however, have been done in younger populations. In this review I focus on screening asymptomatic persons aged 65 and older for cancer. The cancers to be reviewed include breast, cervical, prostate, lung, colon, and ovarian.

Demographics of Older Adults

In 1987 people aged 65 and older comprised 12% of the United States population, for a total of 29 million. Because baby boomers are aging, between 1985 and 2030, the total population is expected to increase by 28%, while the proportion of those aged 65 and older is expected to increase by 128%. In addition, average life expectancy continues to increase. In 1986, the average life expectancy for a man was 71.3 years and for a woman, 78.3 years. The combination of this increasing life expectancy with the aging of the baby boomer cohort results in a great increase in the elderly population.

Cancer is an important disease in older people. According to US all-cause mortality data, cancer is the leading cause of death in women aged 55 to 74, and it is the second leading cause of death in men aged 55 and older and in women aged 75 and older.[3] Cancers with particularly high incidence in the population of older adults include lung, breast, colorectal, and prostate (Table 1).[4]

TABLE 1.—*Annual Cancer Incidence, Per 100,000 Population**

	Incidence by Site					
Group, yr	*Breast*	*Cervix*	*Prostate*	*Lung*	*Colon*	*Ovarian*
40-44	111.67	8.4	0.7	19.1	8.9	5.8
45-49	159.18	8.5	2.9	44.2	18.7	10.6
50-54	185.36	8.8	13.5	88.5	36.3	14.0
55-59	227.26	9.9	41.2	156.0	63.0	18.2
60-64	261.60	10.1	98.6	221.8	102.5	25.1
65-69	297.12	10.9	180.0	287.0	156.7	27.6
70-74	316.45	11.6	275.8	329.9	225.3	32.0
75-79	327.00	12.0	338.1	313.2	309.0	33.5
80-84	336.86	12.3	370.5	274.0	377.9	35.9
85 and older	312.48	16.0	328.8	184.2	417.1	34.5

*From Sondik.[4]

Older adults have an increased incidence of chronic disease and disability. They are twice as likely to see a physician and three times as likely to be admitted to hospital.[5] This increased likelihood of physician contact should present increased opportunities for cancer screening. Health maintenance visits, however, are usually not covered by Medicare A or B, although Medicare coverage has been extended to some screening tests, including mammography.

Cancer Screening in Older Patients

Five characteristics of any disease determine its appropriateness for screening.

- The disease should have a high prevalence among those screened.
- It should have serious consequences.
- It should have a detectable preclinical phase.
- The disease should have a treatment that, when applied to presymptomatic disease, is more effective than if applied after symptoms develop.
- The tests used should be simple, inexpensive, and acceptable with a high sensitivity and specificity.[6,7]

Screening for each type of cancer will be reviewed in the context of these five characteristics.

In addition to disease characteristics, certain characteristics of older persons are also important for cancer screening. Cancer is common in these patients and usually presents at a late stage. Most clinical trials of cancer screening and treatment, however, have enrolled patients younger than 65. In fact, no prospective trials of any cancer screening examination have conclusively demonstrated efficacy in older persons. There are several important issues to consider when screening for cancer in the elderly. Are the treatments for cancer effective, feasible, and acceptable for patients in this age group? How often does screening lead to further evaluation, such as breast biopsy after mammography, that may prove unnecessary yet result in morbidity? Finally, does screening improve the quality of life and functional status of older adults?

Screening for Breast Cancer

Breast cancer has both a high prevalence and serious consequences. It is the most common cancer in women (except for skin) and the second most common cause of cancer death. It has a detectable preclinical phase (detection of a

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mass by clinical examination or mammography), and breast cancers detected and treated at earlier stages have a much better prognosis than those detected later. Finally, the screening tests for breast cancer have proven efficacy in reducing mortality.

A family history of breast cancer in a premenopausal mother or sister is an important risk factor, although it is probably less important in postmenopausal women. The breast cancer risk is doubled if a mother or a sister has breast cancer and is tripled if both a mother and a sister have breast cancer. Other risk factors include early menarche, late menopause, fibrocystic disease (when accompanied by proliferative changes, papillomatosis, or atypical epithelial hyperplasia), and endometrial carcinoma.[8]

Of all newly diagnosed cases of breast cancer, 43% are in women aged 65 or older. The incidence of breast cancer increases progressively with age and almost triples between the ages of 40 and 84 (see Table 1). As the population of older women increases, there will be a large increase in the absolute number of cases of breast cancer.

Most studies of breast cancer screening have not included patients older than 65. Studies that have included older women have shown varying effects of screening. The Health Insurance Plan of Greater New York (HIP) study is one of the landmark studies showing a reduction in breast cancer mortality with annual breast physical examination and mammographic screening. It was a randomized, controlled trial of women aged 40 to 64 observed prospectively for four years. In women aged 50 to 64, there was a 30% decrease in breast cancer mortality 16 years after screening.[9] An analysis of breast cancer mortality distribution, by age, 18 years after trial entry showed that in the cohort of women aged 50 to 64 at entry, breast cancer mortality was significantly lower among those screened. There was a 16.7% reduction in breast cancer deaths among screened women aged 60 to 64 at follow-up 18 years after trial entry.[10]

In a Swedish randomized, controlled trial of women aged 40 to 74, annual mammography, but not physical examination, was studied. At seven-year follow-up, there was a 40% decrease in breast cancer mortality in those aged 50 to 74 at the time of study entry. At eight years' follow-up, breast cancer mortality was decreased by 24% in the screened group.[11] Although women older than 65 are included, a separate analysis for the older group is not possible.

The ideal frequency for mammographic screening in older women depends on the size of the preclinical interval—the period during which early disease is present but symptoms have not yet developed—and on the incidence and aggressiveness of cancers that occur between screening examinations. There is some evidence to suggest that the preclinical interval is longer in women older than 50. A recent analysis of data from the Swedish two-county breast cancer screening trial demonstrated that among women older than 50, few interval cancers were seen in the two years after a screening mammogram, whereas in women aged 40 to 49, the rate of interval cancers in the first and second years following screening was significantly higher.[12]

Screening for breast cancer includes both mammography and clinical breast examination. In both the HIP study and the Breast Cancer Detection Demonstration Project,[13] the screening procedures were clinical examination and mammography. There have been no trials to evaluate annual clinical examination only.[13] Eddy estimates that annual breast physical examinations for ten years can be expected to decrease the chance that a woman will die of breast cancer by about 15 to 40 per 10,000.[14]

Because the incidence of breast cancer increases with age, the absence of data for screening women older than 75 should not preclude screening. The recommendations of various expert organizations are listed in Table 2.[1,15-20] According to a recent cost-effectiveness analysis, because the length of the preclinical interval may be increased in women older than 50, screening low- or average-risk women every two years retains a high proportion of the effectiveness of annual screening.[14] High-risk women should probably be screened annually.

The upper age limit at which breast cancer screening has a significant effect in decreasing breast cancer mortality is not known. Decisions regarding continued screening after the age of 75 should be made by the woman and her physician, based on such factors as co-morbid conditions and associated life expectancy, feasibility and acceptability of surgical therapy, and quality of life. For example, a frail 75-year-old woman on home oxygen therapy for end-stage chronic obstructive pulmonary disease would probably benefit little from screening mammography. The early detection of breast cancer might increase her life expectancy but would not improve her quality of life. In addition, it is unlikely that this patient would be a surgical candidate. In contrast, the early detection of breast cancer in an active older woman with well-controlled hypertension would be more likely to improve the quality of her remaining years of life.

TABLE 2.—*Recommendations Regarding Breast Cancer Screening*

Source	*Recommendation*
American Cancer Society*	Annual breast examination and mammogram for women older than 50
National Cancer Institute†	Annual breast examination and mammogram for women older than 50
American College of Obstetricians and Gynecologists‡	Breast examination and mammogram at a frequency determined by the woman's physician
American College of Physicians§	Mammogram from age 50-59 on a "routine basis" and age 60 and older with a screening interval chosen by the physician and the patient
American Geriatrics Society‖	Annual breast examination and mammogram every 1-2 years
American College of Radiology¶	Annual clinical breast examination and mammogram in women older than 50
US Preventive Services Task Force#	Annual clinical breast examination and mammography every 1-2 years (until age 75*) unless disease is detected

*From the American Cancer Society.[15]
†From the National Cancer Institute.[16]
‡From the American College of Obstetricians and Gynecologists.[17]
§From the American College of Physicians.[18]
‖From the American Geriatrics Society.[19]
¶From the American College of Radiology.[20]
#From the US Preventive Services Task Force.[1] Although the US Preventive Services Task Force recommends mammography annually or every 2 years until age 75, the upper limit at which breast cancer screening no longer has a significant effect in decreasing breast cancer mortality is unknown.

Mammographic screening rates remain low in older women. Even though they have a higher incidence of breast cancer, they are screened less often than younger women.[21] Furthermore, a recent community survey by Harris and colleagues showed that younger women were more worried than older women about breast cancer and assessed their risk as higher, attitudes that were generally associated with higher mammography rates.[22] To increase mammographic screening in the older age group, patients and physicians must be educated.

Screening for Cervical Cancer

Worldwide, cervical cancer is the second leading cause of cancer death for women. In the United States, the incidence of cervical cancer is much lower (see Table 1). About 4,400 deaths from cervical cancer (compared with 46,000 from breast cancer) are expected to occur in 1992.[3] Despite the low incidence, however, cervical cancer is appropriate for screening because of its long preclinical phase and the availability of a simple and inexpensive screening test. Finally, the early detection and treatment of the precursors of cervical neoplasia can substantially decrease the incidence of invasive cervical cancer.

Risk factors for cervical cancer include sexual promiscuity and early age at first intercourse. In contrast to breast cancer, there is a low incidence of cervical cancer after age 65, but older women are less likely to have been previously screened. In fact, 15% of women aged 65 to 74 and 38% of women older than 75 have never had a Papanicolaou smear.[23]

Most studies showing that the incidence of invasive cervical cancer can be significantly decreased by cervical cancer screening have been done in younger populations. Because of the long preclinical interval, patients with two previous normal smears are at low risk for five years. A woman with a history of adequate screening gains little from screening after age 65.

For example, an average-risk 65-year-old woman who has been previously adequately screened (every 3 years for at least 12 years) is screened every three years for an additional four examinations. This decreases her chance of death from cervical cancer by about 18 in 10,000, increases her life expectancy by about three days, and costs about $52,241 per year of life saved.[24] This is in contrast to a calculated cost per year of life saved of $4,850 for biannual mammography in women aged 50 to 70.[25] Hence, a key to determining the frequency of screening in an older population is the frequency of previous screening.

Indigent women, who are at increased risk, are less likely to have had previous adequate screening. A recent study done in an urban public hospital outpatient setting concluded that Papanicolaou smear screening of older low-income women (without a history of adequate screening) was cost effective.[26]

The reliability of Papanicolaou smears in the elderly differs from that in other age groups. Without estrogen stimulation, atrophy and resulting inflammation can be confused with all degrees of dysplasia and even malignancy. Hence, there is a high incidence of false-positive smears in the elderly. Therefore, all abnormal smears should be repeated after a brief course of estrogen.[27]

The preclinical phase of cervical cancer is long, and therefore even if the smear represents a true-positive result, the short delay entailed in repeating the examination after a course of estrogens should not substantially influence the course of disease. Because of vaginal and cervical stenosis, postmenopausal recession of the squamocolumnar junction, and the resulting difficulty in visualizing and sampling the transition zone, false-negative rates may be higher in the elderly as well. In a British study, 50 postmenopausal women were screened with cervical cytologic examinations and colposcopy. Four of the women had evidence of cervical intraepithelial neoplasia by colposcopy, although all had normal cervical smears.[28]

Many organizations have published recommendations for cervical cancer screening (Table 3).[1,29,30] Women with a history of previous adequate screening probably do not benefit from screening after age 65. Older women without a history of adequate screening should probably be screened every three to four years. It has been argued by some that the pelvic examination in older women, done in association with Papanicolaou smear screening, may result in the detection of other pelvic disease. There is no evidence that such detection leads to an improved clinical outcome.

Screening for Prostate Cancer

The efficacy of screening for prostate cancer in men is not as well established as that of screening for breast and cervical cancer in women. With respect to prevalence, prostate cancer qualifies as a disease appropriate for screening. Prostate cancer is the most common cancer in American men and has the third highest cancer mortality rate.[3] Of note are the particularly high incidence and mortality in African Americans,[31] which persist even after adjusting for socioeconomic status.[32] The incidence of prostate cancer among African Americans in Alameda County, California, is 100.2 per 100,000 compared with 0.8 cases per 100,000 in Shanghai, China.[31] Furthermore, the age-adjusted prostate cancer death rate is 23.7 for all races compared with 46.8 for African Americans.[34]

For most men, however, prostate cancer does not have

TABLE 3.—*Recommendations Regarding Cervical Cancer Screening*

Source	*Recommendation*
American Geriatrics Society*	Pap smear every 1-3 years in those without previous regular screening; asymptomatic women who have had several normal Pap smears may no longer need them after age 65.
Consensus†	Annual Pap smear for all who are or have been sexually active or who are age 18 or older; after 3 or more normal smears, they can be done less frequently if recommended by physician
US Preventive Services Task Force‡	Pap smear every 1-3 years, depending on risk factors; may stop at age 65 if several past smears were normal

*From the American Geriatrics Society.[29]

†From Fink.[30] Consensus group includes American Cancer Society, National Cancer Institute, American Medical Association, American Nursing Association, American Association of Family Practitioners, American College of Obstetricians and Gynecologists, and American Medical Women's Association.

‡From the US Preventive Services Task Force.[1]

serious consequences. A large number of cases of prostate cancer are found at autopsy or incidentally at transurethral resection of the prostate, but it is estimated that only 1 in 380 men with histologic evidence of prostate cancer die of it[33] and that 9 of 10 prostate cancers remain clinically asymptomatic for decades.[31] Although prostate cancer can metastasize, patients with metastatic prostate cancer are often asymptomatic.

The disease should have a treatment that when applied to presymptomatic disease is more effective than if applied after symptoms develop. This may be true for prostate cancer but only if detection by screening is of stage A or B disease, as there is no effective curative treatment of stage C or D.

The disease should have a detectable preclinical phase. The preclinical phase of prostate cancer is not well understood. Some prostate cancers are indolent, even when advanced, whereas some are aggressive, with early metastases before an abnormality is detectable on a rectal examination. Thus, even if asymptomatic prostate cancer is detected by digital rectal examination, this does not ensure that the cancer is at an earlier stage and hence more likely to be curable. In contrast, an asymptomatic breast cancer lesion detected by mammography is much more likely to be at an early stage and hence more amenable to treatment.

The tests should be simple, inexpensive, and acceptable with a high sensitivity and specificity. At present there are three proposed screening tests for prostate cancer. Rectal examination is simple, cheap, and (probably) acceptable. Its sensitivity is estimated at about 70% in men with obstructive bladder symptoms but is only about 33% in asymptomatic persons.[1] Transrectal ultrasonography is still considered experimental, and most studies have been done on those with suspected or confirmed prostate cancer. Tumor markers are in general not useful for screening. Prostatic acid phosphatase has a sensitivity of only about 20% to 45%. Prostate specific antigen is sensitive but not specific, as the levels are often also elevated in patients with benign prostatic hypertrophy.[35]

To date, the results of prostate cancer screening have been disappointing. There is no evidence that disease detected through screening has a better prognosis. Although some studies have shown that screened populations are more likely to have stage A or B cancer, there is no evidence of improved mortality. The recommendations of various expert groups are summarized in Table 4.[1,16,36,37] The American Geriatric Society, American Cancer Society, and the National Cancer Institute recommend an annual rectal examination. The US Preventive Services Task Force states that there is insufficient evidence to recommend for or against screening for prostate cancer with an annual digital rectal examination. Because rectal examination is simple, inexpensive, and acceptable (though not very sensitive), with few adverse effects, and while we await conclusive data about the efficacy of screening for prostate cancer, it is probably reasonable to do an annual rectal examination, especially in African-American men in whom the incidence and mortality are so high.

Screening for Lung Cancer

Lung cancer is the most common cause of cancer death in both men and women. Its incidence increases with age, reaching a peak annual incidence of 329.9 cases per 100,000 population in the 70- to 74-years age group (see Table 1). Although lung cancer is a prevalent disease with serious consequences, it does not fulfill other important screening criteria.

To be appropriate for screening, a disease should have a detectable preclinical phase and the treatment of presymptomatic disease should be more effective than if applied after symptoms develop. Lung cancer detected and treated early, when the tumor is still localized, has a better prognosis than that detected at a later stage. In theory, then, the early detection of stage I tumors through screening could potentially prolong survival. But there is no evidence that screening leads to the detection of earlier stage disease, even in high-risk groups. In fact, in the Mayo Clinic (Rochester, Minn) Lung Project, the screening of male smokers every four months for six years with both chest roentgenograms and sputum cytologic examinations had no effect on the number of inoperable cases, the number of cases detected in the late stages, or the number of deaths from lung cancer.[38]

In addition, the current screening tests in use for lung cancer are neither sensitive nor specific. Chest x-ray films have an estimated false-positive rate of from 0% to 10%. In an early Memorial Sloan-Kettering Cancer Center (New York) study, 10% of patients had abnormal chest roentgenograms that led to additional studies, such as bronchoscopy and fine-needle aspiration, to rule out lung cancer; 100 patients were evaluated per cancer found.[39]

There is good evidence that screening for the early detection of lung cancer has no effect on prognosis. Hence, many major organizations including the National Cancer Institute, the American Cancer Society, the United States Preventive Services Task Force, and the American College of Radiology agree that screening for the early detection of lung cancer is not justified. Rather than focusing on the treatment of lung cancer, clinicians' efforts should be directed at primary prevention—urging young people not to smoke and counseling older ones to stop smoking.

Screening for Colorectal Cancer

Colorectal cancer is the second most common form of cancer; 156,000 new cases are estimated to occur in 1992.[3]

TABLE 4.—*Recommendations Regarding Prostate Cancer Screening*

Source	*Recommendation*
American Cancer Society*	Annual rectal examination
National Cancer Institute†	Annual rectal examination
American Medical Association‡	Transrectal ultrasound is investigational
US Preventive Services Task Force§	Insufficient evidence to recommend for or against digital rectal examination; transrectal ultrasound and the use of tumor markers are not recommended

*From the American Cancer Society.[36]
†From the National Cancer Institute.[16]
‡From the American Medical Association.[37]
§From the US Preventive Services Task Force.[1]

TABLE 5.—*Recommendations Regarding Colorectal Cancer Screening*

Source	*Recommendation*
American Cancer Society*	Annual fecal occult blood testing and flexible sigmoidoscopy every 3-5 years after 2 initial examinations a year apart for persons older than 50
National Cancer Institute†	For those at high risk, air-contrast barium enema or colonoscopy every 3-5 years Annual fecal occult blood test and sigmoidoscopy every 3-5 years for "case-finding" in asymptomatic persons
US Preventive Services Task Force‡	Insufficient evidence to recommend for or against fecal occult blood testing or sigmoidoscopy in asymptomatic individuals. Screening those at high risk may be "clinically prudent"

*From the American Cancer Society.[40]
†From the National Cancer Institute.[16]
‡From the US Preventive Services Task Force.[1]

The incidence increases markedly with age, with the highest in persons aged 85 years and older. Important risk factors include inflammatory bowel disease, familial polyposis, a family history of colorectal cancer, and a personal history of breast, endometrial, or ovarian cancer. Approximately 58,300 deaths from colorectal cancer are expected to occur in 1992; substantial morbidity includes that related to colostomies, surgical therapy, radiation therapy, and chemotherapy.

The treatment of early-stage disease is associated with a better prognosis than that of late-stage disease. Those who present with localized disease have a 74% ten-year survival rate, as compared with those who present with disseminated disease, who have a 5% ten-year survival rate. Colorectal cancer does have a preclinical phase—localized disease, such as polyp or adenoma—that can be detected by screening.

The central issue in screening for colorectal cancer involves the screening tests (Table 5).[1,16,40] Ideally a screening test should be simple, inexpensive, and acceptable. The screening tests available for colorectal cancer include digital rectal examination, fecal occult blood testing, and various types of sigmoidoscopy. The digital rectal examination is simple and acceptable, but only about 10% of colorectal cancers develop in the area that can be reached by an examining finger. Even if the digital rectal examination was extremely sensitive, 90% of cases of colorectal cancer would be missed using this method alone.

Fecal occult blood testing is simple, cheap, and acceptable but has a high false-positive rate. It has been estimated that from 1% to 5% of unselected persons will have a positive fecal occult blood test.[41] Of those with positive tests, 10% will have cancer and 20% to 30% will have adenomas. The positive predictive value of fecal occult blood testing for detecting cancer has been estimated at 5% to 10%.[1] Because about 20 ml of blood loss per day is needed for a persistently positive fecal occult blood test, there is a high false-negative rate as well. At present, clinical trials are evaluating the effectiveness of fecal occult blood testing in reducing mortality.

Visual examination of the colon is the most effective way of detecting colon cancer. Sigmoidoscopy and colonoscopy have disadvantages, however, especially patient discomfort. In addition, because most colonic polyps will not develop into malignancy, there is a high false-positive rate. Perforation, although rare, is a serious iatrogenic complication. Finally, sigmoidoscopy is expensive, and the cost of doing annual sigmoidoscopies in all persons older than 50 would be prohibitive.

At present, there is no direct evidence to support or refute screening for colorectal cancer, although indirect evidence suggests that screening with various tests can decrease the disease-related incidence and mortality. Eddy presents a mathematical model of screening in which performing endoscopic evaluation or barium enemas at three- to five-year intervals preserves 90% of the effectiveness of annual examinations with much less inconvenience and cost.[41]

Because of the lack of definitive evidence, decisions about colorectal cancer screening should be made on an individual basis. There are several important factors to consider. First, what effect will a diagnosis of colon cancer have on a person's quality of life and functional status? The early diagnosis of colon cancer in an otherwise healthy 75-year-old man will probably have more effect on quality of life than a similar diagnosis in a person with end-stage congestive heart failure. Second, because any positive screening test will lead to further evaluation, such as flexible sigmoidoscopy after a positive fecal occult blood test, how acceptable is that for the patient? Third, if cancer is discovered, are the treatment options, such as surgery or chemotherapy, acceptable, feasible, and effective? Finally, the screening threshold should probably be lower for persons at higher risk for colorectal cancer, for example, those with a positive family history or a history of inflammatory bowel disease.

Screening for Ovarian Cancer

About 21,000 new cases of ovarian cancer will be diagnosed in 1992.[3] Although this incidence is substantially less than that for either breast or colon cancer, the incidence does increase with age. The disease is most common in women older than 60 years. Furthermore, it has the highest mortality of any of the gynecologic cancers. Risk factors include a family history of ovarian cancer and increased ovulatory activity, including nulliparity, late first pregnancy, and late menopause.

About two thirds of women with ovarian cancer present with advanced disease. Survival is related to the stage at diagnosis and is specifically related to the size of the tumor after treatment. Various treatments appear to be more effective in reducing the size of residual tumor when ovarian cancer is detected early.[42] This suggests that screening for the detection of early disease would be efficacious.

None of the available screening tests for ovarian cancer are appropriate for screening asymptomatic women. Although the pelvic examination is simple and inexpensive, ovarian cancer detected by this method is usually advanced. Malignant ovarian cells may be detected on a Papanicolaou smear, but the sensitivity is low. Cytologic examination of peritoneal lavage fluid obtained by culdocentesis is impractical for routine screening.

The use of tumor markers, especially CA 125, is an area of present controversy. Although CA 125 levels are elevated in late-stage ovarian cancer, it is not known if they are suffi-

ciently elevated in the early stages to be appropriate for screening. In addition, CA 125 levels are elevated in many persons with benign masses, as well as in those with non-gynecologic cancers. Finally, there are minimal data regarding CA 125 screening in asymptomatic women.[1]

Another possible screening method for ovarian cancer is ultrasonography of the pelvis. Although ultrasound is sensitive and specific, because of the low prevalence of ovarian cancer in the general population, the positive predictive value is low. Jacobs estimated that in screening 100,000 women older than 45 years, 40 cases of ovarian cancer would be found, but there would be 5,398 false-positive results and an estimated 160 complications due to diagnostic laparoscopy.[43]

In summary then, given the limitations of available screening tests and the lack of direct evidence that screening for ovarian cancer improves the end result, there are no recommendations for routine screening for ovarian cancer in asymptomatic women. Although the United States Preventive Services Task Force recommends that it is "clinically prudent to examine the uterine adnexa when performing gynecologic examinations for other reasons,"[1] there are at present no data to support the use of other screening tests in asymptomatic persons.

Summary and Conclusions

Screening for certain types of cancer can decrease disease-related mortality. Although cancer is common in older persons, most studies of cancer screening have been done in younger populations. While awaiting the results of prospective trials of cancer screening in an older population, we can carefully extrapolate the results of cancer screening in younger populations.

Available data suggest that screening for breast cancer and cervical cancer can substantially reduce disease-related mortality. Although conclusive data are lacking about the efficacy of screening for prostate cancer, because of its high incidence, it is probably reasonable to do an annual rectal examination, especially in high-risk persons such as African-American men. Screening for lung cancer has been shown not to alter outcomes, and hence the routine screening of asymptomatic persons is not recommended. The early detection of colorectal cancer can improve the outcome, but the available screening tests have several limitations, including high false-positive rates, costs, and patient discomfort. Hence, decisions about colorectal cancer screening should be made on an individual basis. For ovarian cancer, there is no evidence that the detection of early disease by screening is associated with better results.

When making any decision about cancer screening, physicians must weigh the risks and benefits for each patient. These risks and benefits include factors such as co-morbid diseases and associated life expectancy, the feasibility of surgical intervention, the acceptability of cancer treatments, and, most important for the elderly, the effects of screening and the resulting diagnostic evaluations and therapies on the quality of life.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Articles

Disruptive Medical Patients
Forensically Informed Decision Making

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Patients who disrupt medical care create problems for physicians. The risks are not entirely clinical. Although these patients may compromise sound clinical judgment, some are also litigious and express their dissatisfaction in legal or other forums. It then becomes necessary for treating physicians to be aware of the legal and ethical boundaries of their patient care responsibilities. Some disruptive patients are treated by setting limits, which is usually affirmed by health care agreements. A hospital review board may advise clinicians on these agreements and on the management of disruptive patients. If termination of the physician-patient relationship is considered, physicians must follow proper protocol. We examine these forensic considerations and place them in the context of malpractice. Communication, consultation, and documentation are the key elements in reducing liability.

(Sparr LF, Rogers JL, Beahrs JO, Mazur DJ: Disruptive medical patients—Forensically informed decision making. West J Med 1992 May; 156: 501-506)

Physicians may find themselves in the uncomfortable situation of providing care to a disruptive medical patient whose conduct interferes with the exercise of clinical judgment and effective treatment. In these situations, physicians are often unclear about their legal authority to redefine, set limits on, or even terminate their professional relationship with the patient. Issues include the contractual nature of the physician-patient relationship and the legal and ethical boundaries of a physician's patient care responsibility.[1]

By "disruptive patients," we are referring to patients whose behavior interferes with a physician's ability to give health care. For example, disruptive patients may recklessly disregard their medical needs, provide distorted or erroneous information, or engage in abusive, obstructionist behavior that undermines not only their health care but that of others. Most of these patients have joined that medical pantheon of undesirables inhabited by "crocks,"[2] "dirtballs,"[3] "hateful patients,"[4] "gomers,"[5] and "problem patients."[6] Their behavior clashes with the machinery of ordinary health care operations. Medical center administrators may become aware of them through patient or staff complaints, incident reports, lawsuits, or congressional inquiries.[7] In these instances, appropriate action may include communicating clear expectations to the patient and enforcing limits. Because limit setting is not common and occasionally heightens the risk for bad results, physicians sometimes fear being held liable for some putative failure to use standard practice that can be shown after the fact to have contributed to patient injury.

In an earlier study,[8] we discovered that 25% of the patients who caused major disruptions of patient care at our hospital were responsible for 38% of the incidents, including most of those in which injuries occurred or weapons were used. Although there have been many authoritative suggestions[7,9-13] regarding managing disruptive patients, in a few instances the appropriate action may be denying access to care even though the patient has a treatable medical condition.

Unilateral termination of a continuing physician-patient relationship is legally possible, but the physician must give the patient adequate time and opportunity to find another source of care. This may not be a problem in areas well served by medical facilities, but when the patient has inadequate financial resources or no alternative treatment facility, the problem is more complex. It is particularly difficult when the patient's condition is severe, chronic, or requires regular medical attendance. Failure to follow proper protocol may result in ethical charges against the physician, and, if harm comes to the patient, a lawsuit.[14]

In this article, we consider issues concerning individual practitioners. As background, we provide a short review of basic elements of malpractice law, followed by a discussion of forensic principles regarding patient abandonment. We conclude by discussing methods to reduce liability.

Coordinated Care Review Process

Review Board

It is the policy of our medical center (Department of Veterans Affairs [VA] Medical Center) to make reasonable efforts to provide care to disruptive outpatients. Recently the medical center formed a multidisciplinary coordinated care review board (CCRB) to provide consultation to practitioners and administrative staff with patients who are grossly uncooperative with medical care. In the first three years of operation, we have had 75 patients referred to this board. Although we found no data to show that disruptive patients are more litigious than other patients, we have discovered that approximately 30% of the patients referred to the CCRB have made formal complaints to third parties—congressional delegations or VA service organizations—about their care. We have noted previously that in the VA system congressional inquiries have partially evolved into an extralegal mode of litigation.[15] This was a primary reason for the initial formation of the CCRB.

Patients referred to the coordinated care review board are

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ABBREVIATIONS USED IN TEXT

CCRB = coordinated care review board
VA = [Department of] Veterans Affairs

typically medical or surgical patients who need care, are not willing to have psychiatric intervention, or have behavioral problems that interfere with medical treatment. Some of the patients have traditional psychiatric disturbances as well as medical problems. They may have personality traits that lead them to rebel against or defeat the instructions of their health care professionals. They may attempt to manipulate the system to obtain additional compensation, controlled substances, or simply food and shelter; or they may have grown angry at the inability of staff to provide relief from their long-term discomforts.[7]

The review board, which includes psychologists, physicians, a lawyer, nurses, and administrators, makes suggestions to practitioners about patient management, the development of physician-patient health care agreements, and the advisability of terminating the physician-patient relationship. This board and other similar review bodies, whether in private or public settings, are usually made up of existing medical center staff members who are willing to devote extra time to improving hospital safety.

At our facility, patients usually come to the attention of the CCRB through the office of the chief of staff. Previous incidents and efforts to deal with a problem must be well documented before a referral is accepted. This ensures that only truly difficult patients are referred and that data on such patients are sufficiently complete to guarantee a useful consultation.[7] Patient referral to the board must follow four criteria:

- The patient's failure to comply with assessment or treatment poses a substantially increased risk of morbidity or mortality—or both.
- The patient's behavior has involved the repeated use of intimidation (for example, verbal abuse or litigation threats).
- The problem behavior is well documented in the medical record.
- The physician has tried to resolve the problem.

Report of Cases

Case 1

The patient, a 75-year-old man with a history of chronic obstructive pulmonary disease and alcohol abuse, was referred to the CCRB because of noncompliance with treatment. He had many admissions to the hospital that were characterized by a lack of cooperation with discharge arrangements. Usually, after spending his VA disability money, he would come back to the hospital in dire medical condition and need to be readmitted. During admissions he was often verbally abusive toward staff members. Among recommendations by the board was pursuit of a fiduciary arrangement so that the patient's funds and consequently the patient could be better managed.

Case 2

The patient, a 46-year-old man with chronic knee pain, deep venous thrombosis with recurrent pulmonary emboli, and atrial fibrillation, had a long history of noncompliance with both warfarin sodium (Coumadin) therapy and follow-up clinic appointments. At the suggestion of the review board, he was sent a health care agreement that he signed and returned. Afterward, his behavior improved.

Case 3

The patient, a 35-year-old man, had chronic right knee pain. He had been seen by many orthopedic surgeons and, despite a lack of notable findings on x-ray film or arthroscopy, continued to have pain and to insist that his physicians were missing something. He was abusive toward hospital staff, threatened to write his congressional representative, and wanted VA-authorized fee-basis (private) care. After unsuccessful attempts to mediate the situation, the patient was sent a health care agreement. Responding to the language of the agreement, the patient wrote back requesting a signed statement by his physicians that they would not threaten him or use abusive language toward him. The chief of staff responded, acknowledging the responsibility of all physicians to treat patients with respect. The patient never returned the health care agreement and was subsequently sent a notice terminating his eligibility for routine hospital care.

Case 4

The patient, a 63-year-old man with sinusitis, was convinced that all VA physicians were incompetent and that no one had ever treated him properly. His clinical history included many documented instances of verbal abuse toward staff, complaints, and behavioral incidents. Because of the incidents (15 in all), the patient had a behavioral emergency flag on his records (a computer warning to staff about repetitively violent patients).[8,9] The patient had taken his complaints to his representative, his senator, and the hospital's chief of staff. He demanded private fee-basis care because of his dissatisfaction with VA treatment. He signed a health care agreement but complained bitterly about it and had his service officer write a letter of protest to the hospital director. The patient ultimately moved to another area and was sent a letter acknowledging his move and wishing him well. A copy of the letter was sent to his senator.

Case 5

The patient, a 67-year-old former prisoner of war, had 15 service-connected medical disabilities. His two primary problems were diabetes mellitus and hypertension. He had sought help from many health care professionals, had refused most treatment recommendations, and had been noncompliant with outpatient or inpatient care. He had written letters to the VA's chief medical director, filed a personal injury claim against the VA, and had written his representative. He was sent a health care agreement, which he signed, and a letter from the chief of staff designating a single physician for him and suggesting a meeting with that physician, a staff psychologist, and the patient's service officer. Initially, there was some improvement in the patient's behavior.

Physician-Patient Agreements

Discussion with the CCRB helps clinicians clarify what has gone wrong in the physician-patient relationship. Although not all the cases discussed had successful results, explicit plans were developed to try to rectify the situations. Usually with the help of the review board, clinicians with problem patients are advised to first form a treatment agreement with the patient, particularly when there is a complex

interplay among biologic, psychological, and social dimensions of an illness. The board may help physicians see the patient as "sick" rather than "bad." A physician-patient agreement may identify clinical problems and broaden options for their resolution. A sample health care agreement and cover letter are shown in Figure 1.

If no primary care physician has been clearly designated, the board helps appoint one. The emergency department staff is briefed about the nature of the agreement, as are other concerned personnel, such as pharmacists. In the event of a new incident, the patient is referred immediately to the primary care physician, who, with the support of the chief of staff, enforces the agreement.[7]

Sometimes, however, formal contracts hinder communication. Physician-patient agreements may be reflected merely by a medical record note signed by the physician and patient with a copy given to the patient. Whether formal or informal, these agreements may be clinically and legally beneficial and may constitute an enforceable contract, although, as discussed below, the physician should still ensure that all proper steps are taken before terminating the therapeutic relationship.

The physician-patient relationship may fulfill the elements of a legal contract if there is an offer to do something by one party, an acceptance of that offer by another, and "consideration" (that is, a payment or another act of value)

A

Dear _____:

The medical center director and I have discussed the concerns of you and your physician regarding the recent difficulties in your medical care. To rectify this problematic situation, we have decided that we can best provide your care through continuity. Dr John Doe has agreed to be your physician.

This medical center fully intends to work with you, but your cooperation will be essential. To clarify the way in which this care will be carried out, we have outlined the attached health care agreement. Should you decide to continue your medical care at this medical center, please sign the agreement and return it to me in the enclosed envelope. After receiving this signed agreement, Dr John Doe's office will call you to make an initial appointment.

In the event you elect not to seek further care for your health problems at this medical center, we will no longer provide regular medical care or medications. If I do not receive a signed copy of the enclosed health care agreement from you in the next 30 days, I will assume that you no longer desire care at the medical center.

We look forward to joining with you in managing your health care, should you choose to do so at this medical center.

Sincerely,

_____, MD
Chief of Staff

B

The medical center would like to provide you with comprehensive health care. This care will include

- Scheduled visits with Dr John Doe, who will serve as the coordinator of your medical care.
- Medication as prescribed by Dr John Doe.
- Consultations with other care providers, as requested by Dr John Doe.
- Diagnostic and treatment procedures, as ordered by Dr John Doe.

To provide appropriate medical care, your cooperation is necessary. Your cooperation will be demonstrated by your agreeing and adhering to the following points:

- I will limit my contact with this medical center to scheduled appointments with Dr John Doe, except for immediate life-threatening situations, in which case I may be seen in the emergency department. When I or my family members have questions about my health care, we will contact my primary nurse, _____, RN, no more than once per week.
- I will notify the clinic at least 1 day before missing any scheduled clinic visit.
- I will participate in the evaluation and treatment plans as agreed to with Dr John Doe.
- I will inform Dr John Doe about all health care and medication I receive from sources other than the medical center and agree to any communication between health care providers about my care.
- My family and I will treat the staff of this medical center with respect and demonstrate that respect by refraining from loud, abusive, or threatening language or behavior.
- I understand that the medical center cannot safely provide routine medical care if I fail to comply with any component of this agreement. Should I fail to comply with this agreement, the medical center will no longer provide regular medical care or medications.

My signature below indicates my agreement with this plan.

_____ _____ _____ _____
Date Witness Date

Figure 1.—A health care agreement describing the responsibilities of both parties can help the physician and patient to define their relationship. At our medical center, we use the cover letter **(A)** and the health care agreement **(B)** shown.

that makes the agreement more than a gift or nonbinding statement of intent.[16] Even if there is no written agreement, the court may find that a health care contract has been formed because it was "manifested by conduct" of the respective parties.[17] When the physician and patient agree, there is no need for negotiation, and the encounter runs smoothly without a formal agreement. But sometimes the situation is less clear.[18]

In a legal sense, unilateral severance of the physician-patient relationship by the physician when there is still need for continuing medical attention may constitute a breach of contract or a tort, either of which is commonly termed patient abandonment.[19,20] Abandonment in the classic sense involves active intent by the physician to improperly terminate the physician-patient contractual relationship. If there is no such intent and, instead, the physician through inattention and delay provides inadequate care that causes patient injury, it is termed constructive abandonment and the physician may be nonetheless liable. Physicians who have inappropriately terminated patient care are usually sued for negligence rather than breach of contract, in part because physicians generally have insurance coverage for professional negligence but not breach of contract.

Even if a patient fails to comply with a written physician-patient agreement, it would be legally risky for a physician to terminate care without additional notice and an opportunity to find alternative care. Courts could rule that the agreement does not bind the patient or relieve the physician of the usual obligations, because such an agreement may be a "contract of adhesion." For example, if an agreement is not truly bargained but the physician, in effect, compels the patient to accept the agreement to get needed care, the court may not enforce it. Courts are reluctant to enforce contracts that are not the result of bargaining between parties in similar positions of authority. Thus, the physician cannot safely assume that a breach of the agreement by the patient allows the physician to terminate summarily the professional relationship.

Despite these cautions, we think an explicit agreement, formal or not, will strengthen a physician's legal position. In the event of a lawsuit, the agreement would help the physician prove reasonable and responsible behavior by clearly defining the patient's role in allowing the physician to provide adequate care. Certainly a judge or jury would respond favorably to the clear documentation and prudent approach reflected in such an agreement.

Patient Responsibilities

The physician must use the patient's concept of the problem and requested intervention as the starting point.[21] The patient's responsibility is to define the problem and the type of intervention sought from the physician.[18] The fundamental principle of medical practice is a relationship of trust between physician and patient. This relationship requires that both be aware of and assume the obligations inherent in their respective responsibilities.

Patients carry a responsibility to reflect the circumstances, symptoms, and events honestly and accurately and to consider the recommendations provided by their physicians. Physicians in turn are obligated to define and develop a course of therapy in a patient's best interest under the circumstances described and manifested by the patient.[22] If patients do not provide accurate and complete information and if they do not cooperate with treatment, physicians usually will not be held liable for damages resulting from a patient's actions. Physicians' conclusions can be no better than the information provided.

Medicolegal Background

Elements of Malpractice

Abandonment is a type of malpractice described under civil law as a negligent tort. A tort is a civil wrong, as opposed to a criminal wrong, perpetrated by one citizen against another. Rules governing tort liability were traditionally set by common law—that is, by an accumulation of court decisions about principles of liability that are not based on statutes. Many state legislatures have now enacted statutes defining elements of various types of torts.

In a typical medical malpractice lawsuit, the plaintiff has the burden of proof to show that the physician had a legal duty of care to the patient, that the physician breached that duty, and that the breach caused injury to the plaintiff.

A physician acquires a duty to a patient by offering or providing care. It is not necessary to have initiated formal, long-term treatment for a duty to exist. A duty to provide care can be terminated by mutual agreement of the parties or, in some instances, by unilateral action. If the patient needs further care, however, the physician's duty continues until the patient is referred or given time to transfer to another treatment source.[23]

Abandonment as a Cause of Action

In most situations, entry into the physician-patient relationship is discretionary for the physician, but once the relationship is established, its continuance is not entirely discretionary.[24,25] Theoretically, in most nonemergency situations, treatment is provided by choice until the patient no longer needs care or dismisses the physician. Although the courts respect a physician's right to withdraw from a case, if a need for service persists, the physician is bound to give notice to the patient of the proposed termination and afford ample opportunity for securing other medical attendants of choice.[26] Unilateral termination is considered abandonment when these obligations to provide notice and alternative treatment options are breached.

Although abandonment is a legal cause of action recognized in every state, there are variations among jurisdictions. For example, several courts have established that abandonment occurs only when a physician leaves a patient at a *critical time*, without giving reasonable notice or making suitable arrangements for the attendance of another physician. A physician may terminate care even at a critical time, however, if an adequate substitute health care professional assumes care of the patient. In some states, physicians may be liable if they excuse themselves from even routine treatment of a patient without giving notice and a reasonable opportunity for the patient to acquire other medical help or without obtaining the consent of the patient. This standard is more advantageous for the plaintiff patient because there is no need to prove that the physician left at a critical treatment stage.[27] An abandonment claim can be a particularly fertile ground for malpractice litigation when bad feelings are combined with a bad result.[23] Once the act of abandonment is proved, convincing a judge or jury that the abandonment caused injury may be less difficult than proving cause in some other types of malpractice cases.[28]

Whether practicing in a health care institution or a private

office, a physician should be wary of the following situations that have been found to constitute abandonment if adequate substitute care is not found: premature patient dismissal and absenting oneself because of other patients' needs, personal illness, or vacations.[27] A physician who fails to see the patient at intervals necessitated by the patient's condition may be held to have abandoned the patient. A physician may also be liable for abandonment if a patient is dismissed without proper procedure, despite the fact that the patient has failed to pay a bill or to keep appointments, gone to another physician temporarily, unilaterally sought consultation from another physician, or has not followed instructions.[29-31]

We think termination without consent is best accomplished by giving the patient a written notice or sending a registered letter terminating the relationship, suggesting alternative sources of care, and allowing enough time (at least 30 days) for the patient to secure another physician. In some situations, it is advisable for the physician to assist the patient in arranging alternative care.

The case of *Payton versus Weaver* illustrates the authority of health care professionals to terminate physician-patient relationships under appropriate circumstances and by following proper procedures even when the patient has a serious illness.[32] The plaintiff, Ms Payton, was a 35-year-old woman with chronic end-stage renal disease. She lived alone in a low-income housing project and, in addition to having kidney disease, abused alcohol and had been addicted to heroin and barbiturates for more than 15 years. She first began outpatient hemodialysis treatment in 1975 with Dr Weaver, a renal specialist, but she was disruptive, uncooperative, and verbally abusive to staff members. Finally, Dr Weaver sent her a cautionary letter proposing termination of care if her "persistent uncooperative and antisocial behavior" continued. In response, Ms Payton applied for admission to dialysis programs at two local hospitals but was refused. Dr Weaver continued to provide care to her on an emergency basis for an additional year or so, but her behavior did not improve. He then sent her a second letter terminating their physician-patient relationship. Ms Payton filed suit, seeking a court order to compel continuation of treatment. A settlement was reached, resulting in an elaborate health care contract under which Ms Payton agreed to improve her conduct by keeping appointments, refraining from using alcohol and drugs, maintaining dietary restrictions, and cooperating with care providers. When she did not comply with any terms of the agreement, Dr Weaver once again notified her in writing that her treatment would be terminated. Ms Payton instituted a second legal action seeking continuation of treatment. The trial court denied her petition, finding that Ms Payton had not fulfilled her obligations and had actively undermined treatment. The court concluded that Dr Weaver had properly discharged his responsibility to her and that the hospital had not violated her rights by failing to provide care. A stay of the court's judgment was entered to permit Ms Payton to appeal the decision. The appellate court upheld the trial court decision, finding that the physician had behaved according to the highest professional standards.

Reducing Liability

Documentation and consultation are two safeguards against liability. When terminating care, the reasons should be documented clearly and explicitly. Because a physician's judgment may be influenced by hostility to the patient, consultation may be useful. Good-faith referrals or allowing the patient a negotiated return if the problem has been otherwise redressed is possible. Clinicians are not obligated to accept any patient back into full treatment, but patients may be given periodic reevaluations. The one circumstance in which a clinician simply cannot terminate patient care is a state of emergency.[23]

Patients' negligence and assumption of risk are increasingly recognized as defenses in malpractice actions, although this varies from state to state. In pure contributory negligence (or contributory fault), a plaintiff patient's recovery of damages may be barred even when the defendant was at fault if the patient was sufficiently at fault as well. Typical rules for this defense are set forth in *Santoni versus Schaerf*[33]: a patient's negligence "must be concurrent" with, not subsequent to, the physician's; the burden of proof is on the defendant physician; and the key elements are the patient's appreciation of risk and his or her failure to do what a person of "ordinary prudence" would do. The contributory negligence of patients who fail to provide information or cooperate has been affirmed as a defense to malpractice claims by some courts.[34-38]

Many states, however, have adopted some concept of comparative negligence, with degrees of negligence measured in terms of a percentage of fault rather than either-or. An Illinois appellate court defined the relevance of comparative negligence to malpractice actions in *Newell versus Cores*,[39] noting that a patient's refusal of recommended treatment put a physician in a dilemma of giving suboptimal treatment or abandoning the patient. The court charged the jury to consider the nature of the treatment provided, whether this and the preferred treatment were fully explained to the plaintiff patient, and whether the patient knowingly refused the preferred treatment. It noted that comparative negligence is "particularly suited for such a broad-based fact-finding." Some typical limits are stated in *Bellier versus Bazan*[40]: The patient's fault must be concurrent with the physician's; subsequent fault can still mitigate damages, but any reduction in recovery can be negated by the physician's failure to give informed consent.

A forum such as the Coordinated Care Review Board provides clinical consultation to treating physicians. It can help them distinguish between a patient who is simply annoying and one who is actively disrupting the medical system. A patient who decides to terminate care should be cautioned beforehand of the consequences, and this should be documented in the medical record. Otherwise, the patient may file suit on the basis of not being warned about the consequences of terminating treatment.

Writing appropriate letters to patients that discuss possible or actual termination may be difficult. Some court decisions suggest that letters should be explicit when discussing both specifics and consequences of disruptive patient behavior. In *Mortiz versus Medical Arts Clinic*, a plaintiff patient sued a group practice clinic and its administrator for libel after she was sent a letter of notice terminating her clinical care.[41] The plaintiff had previously sued the clinic for malpractice, which resulted in a settlement out of court. Afterward, the clinic sent the patient a letter in an attempt to terminate its professional relationship with her. The patient protested by initiating a defamation suit even though the termination letter had been rather neutral in tone. There was no allegation that the plaintiff either did not have adequate time

to find another physician or had trouble finding one. The majority of the justices on the North Dakota Supreme Court decided that the letter could not be taken to have any defamatory meaning. A dissenting justice, however, wrote that a failure to give reasons for terminating a professional relationship leaves a notice susceptible to a defamatory interpretation. Thus, even though the clinic prevailed, the dissent suggested that a physician's legal position would be stronger if a termination letter were more detailed and explicit, provided that the reasons expressed are accurate and supportable.

Usually, however, when a letter terminating care is sent, there is little discussion of or attempt to list specific patient provocations. There may be clinical reasons to be cautious. Curran suggests that this is a Hobson's choice because even though providing written reasons for termination might be legally prudent, adopting such a practice might provoke more problems with ex-patients than it would avoid.[14] Stating the reasons for termination could cause disputes and lawsuits over the adequacy and truth of the reasons given. To help avoid liability, sensitive letters should be accurate, succinct, and confidential.

The issue of confidentiality, along with informed consent, may be a concern when dealing with disruptive patients because information must be shared among health care professionals and patients must be told of the medical consequences of their actions. Although a thorough discussion of informed consent and confidentiality is beyond the scope of this article, disruptive patients are engaged in public behavior that usually mitigates confidentiality. This latter issue has been debated extensively.[41-45]

Conclusion

From the cases discussed here, it is evident that not all encounters with disruptive patients end successfully. Sometimes either the patient or physician prematurely breaks off the professional relationship. The physician acting either to set limits on the patient or to terminate the physician-patient relationship should do so with full awareness of medicolegal protocol. We describe a hospitalwide interdisciplinary review board that advises clinicians and the chief of staff on the disposition of disruptive patients. Consultation, documentation, and communication are the key elements of reducing liability. In contrast, the physician must avoid unilateral, arbitrary, or vindictive actions when dealing with disruptive patients. While these patients often tax our patience, a consistent, firm, and coordinated approach may allow a heretofore untreatable patient to become treatable.

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Use of Traditional Health Practices by Southeast Asian Refugees in a Primary Care Clinic

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To determine the prevalence of use of traditional health practices among different ethnic groups of Southeast Asian refugees after their arrival in the United States, we conducted a convenience sample of 80 Cambodian, Lao, Mien, and ethnic Chinese patients (20 each) attending the University of Washington Refugee Clinic for a new or follow-up visit. Interpreters administered a questionnaire that dealt with demographics, medical complaints, traditional health practices, health beliefs, and attitudes toward Western practitioners. In all, 46 (58%) patients had used one or more traditional health practices, but the prevalence varied by ethnic group. Coining and massage were used by all groups except the Mien, whereas moxibustion and healing ceremonies were performed almost exclusively by the Mien. Traditional health practices were used for a variety of symptoms and, in 78% of reported uses, patients reported alleviation of symptoms.

The use of traditional health practices is common among Southeast Asian refugees. Clinicians who care for this population should be aware of these practices because they may supersede treatments prescribed by physicians or leave cutaneous stigmata that may be confused with disease or physical abuse. Good patient care may necessitate the use or tolerance of both Western and traditional modalities in many Southeast Asian refugees.

(Buchwald D, Panwala S, Hooton TM: Use of traditional health practices by Southeast Asian refugees in a primary care clinic. West J Med 1992 May; 156:507-511)

Over a million Southeast Asian refugees of at least five major ethnic groups live in the United States today, and over 4,000 more arrive each month from the war-ravaged countries of Vietnam, Cambodia, and Laos (Robert Johnson, International Rescue Committee, oral communication, August 1990). In many Western countries, these distinct ethnic groups are often assumed to represent a single culture or population. Members of these groups are distinguished, however, by factors such as nationality, language, and religion. Values, practices, and norms in these cultures also may differ greatly from each other and from those in Western society. Knowledge about these differences is of particular importance in medicine, where patients' medical beliefs and health practices can result in inappropriate or inadequate treatment. We surveyed Cambodian, Lao, Mien, and ethnic Chinese refugees attending a primary care clinic to learn more about cultural differences in medical beliefs and health practices.

Patients and Methods

Setting

The University of Washington Refugee Clinic is located at Harborview Medical Center, one of the four major teaching hospitals affiliated with the University of Washington School of Medicine. This general internal medicine clinic was established in 1982 to meet the needs of the rapidly growing Southeast Asian refugee population in the Seattle area. Approximately 4,000 clinic visits are made annually, and over 70% of the patients are Cambodian. The staff employs 12 medical interpreters who speak 13 languages. All interpreters finish a one-year community health advocate program designed to train clinical assistants.

Patients

A convenience sample of 20 patients in each of four ethnic groups—Cambodian, Lao, Mien, and ethnic Chinese (10 from Vietnam and 10 from Cambodia)—were interviewed by interpreters during a routine visit. Although not representative of the clinic's population in its ethnic distribution, this sampling strategy of interviewing unselected patients ensured adequate representation of each ethnic group and enhanced our ability to detect differences among them.

The Cambodian, Vietnamese, and Lao refugees had spent time, often years, in camps on the border of Thailand waiting for permission to emigrate. Most refugees from Cambodia and Vietnam are ethnic Khmer or Vietnamese; the minority, ethnic Chinese, are generally better educated and primarily urban. Both groups, as well as the Lao, place a high value on family and adherence to Buddhist principles. Unlike the lowland Lao, the Mien are a tribal people with a distinctly separate culture; they live in scattered villages in the mountainous regions of Laos. Their religion is a mixture of ancestor worship, animism, and Buddhism.[1]

The interpreters collected information on demographics, current medical complaints, medical beliefs, use of specific traditional health practices for current and past medical problems, and attitudes toward Western practitioners. This information was collected using a questionnaire that contained both structured and open-ended questions.* After receiving individualized instruction in its administration, the inter-

*Marjorie Muecke, CRN, PhD, Associate Professor, School of Nursing, University of Washington, and the interpreters in Refugee Clinic, especially Leng Taing, Sarnseng Saechao, Somey Lammittre, Serey Mean, and Thomas Heng, helped with this study. Noel Chrisman, PhD, assisted in preparing the questionnaire. Philip Kirby, MD, helped with photographs.

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preters translated and administered the questionnaire. Patients were asked if they had used any of 21 traditional Southeast Asian health practices we could identify through a review of the literature and interviews with interpreters and a medical anthropologist. For each traditional practice reported, we collected more specific information on how it was performed and by whom, for what problem it was used, and whether it helped. The patient's physician was not present during the interview. Written informed consent was obtained from all patients. Comparisons between populations were tested with the χ^2 statistic.

Description of Selected Traditional Health Practices

Coining is done by lubricating the skin or a coin and then stroking the skin firmly, usually on the torso or extremities, with the edge of the coin, resulting in parallel ecchymotic streaks (Figure 1). *Pinching* uses the same principle, but pressure is applied by pinching the skin between the thumb and index finger to the point of producing a contusion. *Cupping* is performed by placing a small, heated cup on the skin, usually on the forehead or abdomen, and allowing it to cool. This results in negative pressure, which causes a circular ecchymotic area to appear (Figure 2). *Moxibustion* consists of making small, circular, superficial burns, usually on the torso, head, or neck, by touching the skin with burning incense or by igniting a combustible material placed on the skin. Moxibustion may be used with *acupuncture,* which involves placing acupuncture needles over strategic points along energy "meridians" (Figure 3). Using *medicated paper* involves placing small pieces of paper on the skin, often directly over a symptomatic area; the pieces of paper are soaked in an aromatic oil. *Healing ceremonies* are done by a shaman or traditional healer, who performs rituals that may be directed at illness sources such as spirits, ancestors, "wind," and the patient's soul.

Figure 1.—Parallel ecchymoses visible on the skin are the result of coining, in which the skin is stroked firmly with the edge of a lubricated coin.

Results

Patient Characteristics

Characteristics of the study patients are shown in Table 1. The Mien patients were the oldest, and the Cambodian group had the highest proportion of females. Almost half the patients had been in the United States for more than five years, whereas 20% had resided here for less than a year. Of those surveyed, 24% of the men and 2% of the women were employed outside the home.

Reported Symptoms, Beliefs, and Behaviors

Patients reported a variety of symptoms, health beliefs, and behaviors. The most common chief complaints at the study visit were joint pain (15%), headache (13%), gastrointestinal complaints (11%), back pain (10%), and chest pain (9%). There was no correlation between specific symptoms and ethnic background. The cause of their illness was not known by 64% of the patients. In all, 20% of Chinese, 30% of Lao, 40% of Cambodian, and 45% of Mien patients had previously seen other physicians outside the refugee clinic for their chief complaint. Western medicines not prescribed

Figure 2.—In cupping, a small cup is heated and applied to the skin, causing negative pressure as it cools (left) that results in circular ecchymoses on the skin (right).

Figure 3.—Acupuncture involves inserting needles into the skin at strategic points, called energy meridians, in this patient leaving small, pinpoint-sized marks on the skin.

by a clinic physician were being taken by 10% of Cambodian, 15% of Chinese, 20% of Lao, and 30% of Mien patients. In addition, 80% of Mien, 60% of Lao, 40% of Chinese, and 25% of Cambodian patients stated a belief that they would be cured by a refugee clinic physician.

Use of Traditional Health Practices

Of the 80 patients, 46 (58%) had used one or more traditional health practices since arriving in the United States, but the prevalence of use varied greatly among the ethnic groups (Table 2). Women were more likely to report using traditional health practices than men overall (69% compared with 39%, $P < .01$) and within each ethnic group (Lao 18% versus 0%, Cambodian 96% versus 50%, Chinese 64% versus 44%, and Mien 91% versus 67%). The use of these practices was greater in patients from rural areas than in those from towns or cities (81% versus 36%, $P < .001$). The prevalence of use of traditional health practices was not associated with the duration of residence in the United States.

Types of Traditional Health Practices

Coining was the most commonly used traditional health practice among the Cambodians (70%), the Chinese (35%), and the Lao (10%); however, this practice was not reported by the Mien (Table 2). Similarly, massage was used by all groups except the Mien. Coining and massage were the only practices reported by the Lao. Cupping was used commonly by the Cambodians and the Mien but not the other two groups. Moxibustion and healing ceremonies were used almost exclusively by the Mien.

Each of the commonly used traditional health practices was used for a wide variety of symptoms (Table 3). Practices identified by our staff or described in the literature but not reported by our patients included the use of tattoos, holy water, hair cutting, talismans, and steam inhalation.[2-4]

Patients reported that a traditional health practice definitely alleviated their problem in 62 (78%) of 83 reported uses. In only four reported uses were practices entirely unsuccessful in providing relief, and in 14 they were helpful only under certain conditions, such as if the problem was perceived as spiritual. Moxibustion, healing ceremonies, and cupping were least likely to be reported as unqualified successes; only 5 of 11 uses of moxibustion, 3 of 14 uses of healing ceremonies, and 1 of 9 uses of cupping were reported to be entirely successful.

Discussion

Traditional health practices are used commonly by Southeast Asian refugees, including those who have resided in the United States for many years. We documented substantial differences in the prevalence of use of these practices among ethnic groups and between sexes within these groups. The reasons for these differences remain unclear but probably reflect differences in the sophistication of medical knowledge. Populations with a low prevalence of use of traditional health practices may have greater exposure to, and therefore greater acceptance of, Western medical principles. In the case of the Mien, the higher use, particularly for healing ceremonies, may reflect the older age of this population.

There have been few studies examining the use of traditional health practices among Southeast Asian refugees in the United States. Our results are consistent with earlier obser-

TABLE 1.—*Patient Characteristics by Ethnic Group*

Characteristic	*Cambodian*	*Lao*	*Mien*	*Ethnic Chinese*	*Total*
No. enrolled	20	20	20	20	80
Mean age, yr	46	45	57	47	49
Age, %					
18-39 yrs	40	45	10	30	31
40-59 yrs	50	40	40	60	48
>60 yrs	10	15	50	10	21
Female, %	80	55	55	55	61
Residence in native country, %					
Large city	10	70	5	80	41
Town	20	10	5	15	13
Village	70	20	90	5	46
Buddhist, %	84	85	90	88	87
Years resided in US, %					
<1	5	15	21	35	20
1-3	17	20	26	15	19
>3-5	28	5	11	15	14
>5	50	60	42	35	47
Males employed, %	25	44	11	33	24

TABLE 2.—*Patients Using Specific Traditional Health Practices Since Arrival in the United States**

Practice	*Cambodian, n=20*	*Lao, n=20*	*Mien, n=20*	*Ethnic Chinese, n=20*	*Total, n=80*
Acupuncture	--	--	1	1	2
Coining	14	2	--	7	23
Cupping	4	--	5	--	9
Hair pulling	3	--	--	1	4
Healing ceremonies	--	--	14	--	14
Massage	5	1	--	2	8
Use of medicated paper	--	--	1	1	2
Moxibustion	1	--	10	--	11
Use of oils and balms	--	--	--	2	2
Pinching	1	--	2	1	4
Use of teas	1	--	2	--	3
Other	--	--	1	2	3
Any practice (not specified)	17	2	16	11	46

*Many patients used more than one traditional health practice, so the number of practice uses reported may exceed the number of patients for a particular ethnic group.

TABLE 3.—*Patients With Symptoms for Which Selected Traditional Health Practices Were Used*

Symptom	*Caining*	*Cupping*	*Maxibustion*	*Massage*	*Healing Ceremanies*
Body aches	2	--	1	1	--
Dizziness	4	2	--	--	--
Joint pain	1	--	3	--	--
Fever	--	1	1	--	--
Gastrointestinal problems	3	2	4	--	1
Headache	6	1	--	2	--
Myalgias	--	--	--	2	--
Shaking	2	--	--	--	--
Other	2	2	2	2	--
Unspecified health problem	3	1	--	1	13
Total	23	9	11	8	14

vations, which found that Southeast Asian refugees frequently diagnosed and treated themselves and that those from rural areas were more likely to continue practices used in their native country.[5] In one study, root medicines were found in 27% of Lao and 7% of Vietnamese households, and tiger balm was found in 80% of Lao and 54% of Vietnamese households.[6] In another study, 49 of 50 Vietnamese interviewed, including a nursing student and a medical assistant, still performed coining four years after arriving in the United States for a wide variety of symptoms.[7]

Traditional health practices may reflect different beliefs about the causes of illness that have evolved in Southeast Asian cultures.[2-4] Perhaps the prevailing belief is the naturalistic theory, in which diagnosis and treatment involve integrating physical and social factors. "Wind" is thought to cause many minor and major illnesses. Certain foods, such as beef, may carry "wind" and so are avoided. Treatment consists of special diets, medicinal herbs, or coining, which is commonly used to "rub out the wind." A second belief is that certain illnesses are a punishment resulting from the influence of gods, demons, spirits, or malevolent or magical spells. These illnesses are treated by healers or shamans, who negotiate with supernatural forces to remove or alleviate the sickness. A metaphysical explanation (also known as the "hot and cold" or yin-yang theory) is also used to explain illness. In this case, illness is caused by an alteration in the natural balance between hot and cold elements in the universe. To restore balance and harmony, intake of drugs and foods is adjusted. Coining, pinching, or cupping may be done to restore balance by releasing excessive "air"; in cupping, as the cup cools, it is believed to draw the skin and air up and out. Western medicines are generally considered hot, whereas herbal remedies possess cooling properties. Thus, depending on the nature of the illness, Western medicines may be avoided or reduced in dosage.

Little is known about users' perceptions regarding the mechanisms of action of traditional health practices. In our study, a mechanism of action was given in only 26% of reported uses. This is consistent with a survey on coining in which only about half of the respondents were able to cite a mechanism, such as increased circulation or body warmth, facilitation of respiration, or a spiritual connection.[7] Patterns of use in our patients suggest that different traditional health practices may serve the same function because various practices were reported for the same symptom.

In traditional, rural Southeast Asian cultures, herbal remedies, dermal techniques, and exorcistic rituals are the principal forms of medical treatment.[8] More than one treatment is often used for the same illness, either simultaneously or in succession. The aid of a health practitioner is sought if home remedies are not successful, and Western medicine, if available, may be used only when all else has failed. The same

pattern of health care behavior is practiced in urban populations, but healers are used less often and Western medicine more commonly.[8]

The potential benefits of traditional health practices depend on the patient's condition and the type of practice used. For example, their use may provide the sufferer, who may feel helpless, with a sense of partial control. The attention given to patients by those administering these practices is comforting and may itself be therapeutic. In addition, a placebo effect may have a beneficial effect on minor or self-limiting disorders. These practices also may be harmful, however, because further feelings of hopelessness may result if the treatment fails to resolve the condition. This may be exacerbated by the belief that the failure of a given practice is the fault of the patient. More important, using traditional health practices may be detrimental if patients delay seeking medical care for treatable conditions or if the practices include harmful ingredients. Traditional health practices may also involve considerable expense, especially when a healer or shaman is consulted.

Using traditional health practices has resulted in scarring, cosmetically undesirable lesions, spurious accusations of physical abuse, and unnecessary medical evaluations. Clinicians unfamiliar with these practices may suspect abuse when a patient, particularly a woman or child, presents with cutaneous lesions resulting from a traditional health practice (pseudobattering).[9-11] In one such instance, a false accusation of child abuse resulted in the suicide of the Vietnamese father.[11] In our clinic, a Cambodian woman underwent an extensive evaluation for alopecia, including laboratory tests and a dermatology consultation, before it became evident that her hair loss was the result of pulling hair at the crown and top of the head to treat headaches.

Conclusion

Increasing awareness and knowledge of traditional health practices should help physicians appreciate a patient's perception of Western medicine. Physicians should maintain a nonjudgmental attitude toward such practices while seeking information from patients about which traditional health practices and Western medications are being used. Good patient care may necessitate the use or tolerance of both modalities in many Southeast Asian refugees.

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Articles

Purchasing Prescription Medication in Mexico Without a Prescription

The Experience at the Border

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Prescription medication can often be purchased in Mexico without a physician's prescription. United States residents living along the border may have access to dangerous medications by crossing the border and purchasing them in Mexican pharmacies. We sought to determine the extent and frequency of this behavior in a sample of our ambulatory clinic population. Patients from the Texas Tech University Internal Medicine Clinic were surveyed to collect information about their use of medications, use of alternative sources of health care in Mexico, and purchasing of prescription medication in Juarez, Mexico. More than 80% of patients stated they had purchased prescription-type medication at a pharmacy without a physician's prescription. The most common reasons for buying prescription medication in Mexico were because it was less expensive or because a prescription was not necessary. These data indicate a potential for US residents along the border to take medications in an unregulated manner, a practice that could pose problems for health care providers on both sides of the border.

(Casner PR, Guerra LG: Purchasing prescription medication in Mexico without a prescription—The experience at the border. West J Med 1992 May; 156:512-516)

The delivery of health care on the United States-Mexico border presents unique challenges. In terms of disease and illness, the border is not clearly defined. Diseases that are unusual in other parts of the United States, such as neurocysticercosis, are common along the border,[1] while others such as tuberculosis, hepatitis, and infectious diarrhea are found in higher incidence.[2] The proximity of the two nations allows easy access to the health care systems of both countries. For example, curanderos, or faith healers, are an accepted form of alternative health care for many Mexicans and Mexican Americans.[3,4] Herbal medicines, which are used to treat many maladies, can be purchased in Mexico at small shops called "hierberias."[5] Finally, medications that can be sold in the United States only by prescription are obtained easily in Mexican pharmacies without a physician's prescription. Although selling prescription medication without a prescription is technically illegal in Mexico, this practice is widespread.[6] Thus, patients from the United States can cross the border and purchase potentially dangerous medications simply by asking for them at a Mexican pharmacy. Physicians who practice medicine near the Mexican border see this as a common occurrence and occasionally see serious medical complications resulting from this practice.[7]

El Paso (population 515,000) is the largest US city on the border. It is situated on the Rio Grande directly across from Juarez, the largest Mexican city on the border (population 1.2 million). We wanted to determine the frequency with which our El Paso clinic patients were obtaining medications in Juarez. We conducted a pilot study to quantify this behavior and to determine the consequences of it.

Methods

To compile the data for this study, a questionnaire consisting of 21 questions was developed, with 13 additional demographic questions included. The patient population for this questionnaire consisted of outpatients in the Internal Medicine Clinic at the Texas Tech University Health Sciences Center in El Paso. Patients were asked if they wished to participate while in the waiting area of the clinic. Patients were selected nonsystematically for the survey, which was done over a one-month period. The purpose of the questionnaire was explained, an estimate was given of the length of time required to answer the questionnaire, and patients were then asked if they would like to participate.

Participation was voluntary, and no further information was collected from those who refused to take part. Patients who agreed to participate were taken to a private room where the questionnaire was answered using a directed interview technique. The interviewer was a bilingual health care employee who was familiar with medical terminology. The questionnaire was available in both English and Spanish, and patients who could not understand English were interviewed in Spanish. The questionnaire was pretested in a small sample of patients to verify patient understanding and identify ambiguous questions.

The questions were in four categories. One set of questions sought data on patient demographics, while another set of questions gathered information on patients' attitudes about their own medication-taking behavior. Three questions requested information about alternative sources of health care for patients, and the final 13 questions were directed at obtaining information relating to the purchase of prescription medication in Mexico.

Results

Of the 79 patients interviewed, 32 were questioned in English and 47 in Spanish. For questions that could be answered with more than one response, all responses were

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TABLE 1.—*Profile of Respondents to Medication Questionnoire in on El Poso, Texas Clinic*

Characteristic	N	*(%)*
Age, yr ± S.D.	52 ± 17	
Sex		
Male	16	(20)
Female	63	(80)
Race		
Black	3	(4)
White	76	(96)
Ethnic group		
Hispanic	73	(92)
Non-Hispanic	6	(8)
Employment status		
Employed	16	(20)
Unemployed	63	(80)
Financial support		
Spouse	19	(34)
Social Security	22	(39)
Pension	6	(11)
Disability	1	(2)
Family	5	(9)
Social assistance	3	(5)
Health insurance		
None	44	(56)
Medicare	19	(24)
Medicaid	7	(9)
Other	8	(10)
Education—highest level attained		
No formal schooling	1	(1)
3rd grade	7	(11)
6th grade	29	(45)
High school w/o diploma	2	(3)
High school with diploma	14	(21)
College	5	(7)
Other	7	(11)
Country of education		
United States	31	(41)
Mexico	45	(59)
Marital status		
Single	17	(22)
Married	55	(70)
Divorced	7	(8)
Children, no. ± S.D.	4.5 ± 3.0	
American citizenship		
Yes	45	(58)
No	22	(42)

recorded. Not all patients responded to every question. Demographic information is presented in Table 1.

Table 2 shows the responses to questions about patient medication. In all, 70% of the patients stated they took medications on a daily basis, and almost all patients stated they took their medications as they were supposed to (97%), that they believed the medication was effective (96%), and that they preferred to take medication orally (88%).

As expected, most (72%) of the patients stated that they received their health care from a health clinic in Texas (Table 3). None of the patients, however, stated they were using alternative health care delivery systems offered in Mexico, such as a curandero or a sobador (one who heals by physical manipulation). Although none of the patients stated they were attending a health clinic in Mexico, 22% said they saw a private physician in Mexico regularly. The most common reasons for seeking medical care in Mexico were less expensive medical care (42%) and easier access to health care (39%).

Of the patients, 81% stated that they had purchased medications in Mexico at one time or another, and 79% stated they were still purchasing medications in Mexico (Table 4). A total of 55% said they purchased medications in Mexico *at least* several times a year. In all, 69% of the patients stated that they had bought medications in Mexico within the last month, and 28% within the last week. The responses indicated that 75% of the patients purchased medications without a prescription from a pharmacy in Mexico, while 25% did so with a physician's prescription. Of those patients who responded, 72% stated that the medication was recommended to them by an individual other than a physician, that is, a pharmacist, friend or relative, or themselves. In response to the question "Why do you buy medicine in Juarez?" 49% of the patients said that they did so because it was less expensive, and 20% because they didn't need a prescription. When asked "Do you know other people who buy medicines in Juarez?" 81% of the patients answered "yes." The types of medications purchased in Mexico varied (Table 4, Figure 1), but the two most common classes of medications purchased were blood pressure medications and antibiotics.

Only 11% of patients said they had experienced a side effect at one time or another from the medication that they purchased, and two patients (3%) stated they required hospitalization for such side effects. The majority of patients (57%) felt that medications purchased in Mexico and the United States were of equal quality, and most (88%) stated they received advice about side effects and dosage of medications when they bought medicines in either the United States or Mexico. There was no significant correlation between purchasing medication in Mexico and Hispanic ethnicity, employment status, possession of health insurance, education, or citizenship by either the χ^2 or Fisher's exact test.

TABLE 2.—*Potient Attitudes About Medicotions*

Question	*Response*	N	*(%)*
Do you take medication daily?	Yes	54	(69)
	No	24	(31)
What medical problems do you take medications for?	High blood pressure	36	(41)
	Heart disease	5	(6)
	Diabetes	16	(18)
	Arthritis	9	(10)
	Other	21	(24)
Do you take your medication as directed?	Yes	70	(97)
	No	2	(3)
Do you feel the medication is working?	Yes	71	(96)
	No	3	(4)
How do you prefer to take medication?	Orally	66	(88)
	Intramuscularly	5	(7)
	Intravenously	1	(1)
	No preference	3	(4)

TABLE 3.—*Source of Health Care*

Question	*Response*	N	*(%)*
Where do you go for medical care?	Private physician in El Paso	5	(5)
	Private physician in Juarez	22	(22)
	Local clinic	73	(72)
	Clinic in Juarez	0	
	Chiropractor	0	
	Curandero	0	
	Sobador	0	
	Pharmacist in Juarez	1	(1)
Do you receive medical care in Juarez, and, if so, how often?	No	46	(61)
	Yes	29	(39)
	Once/wk	1	
	Once/mo	3	
	Once/yr	6	
	Other	19	
Why do you go to Juarez for medical care?	Less expensive	14	(42)
	Easier access to health care	13	(39)
	Convenience	1	(3)
	Physicians and nurses relate better to you	2	(6)
	Other	3	(9)

Discussion

Only one report that we are aware of has examined medication use by residents of the United States purchasing their medications in Mexico. Tabet and Wiese[8] surveyed patients in a rural health clinic 28 miles from the US-Mexican border and in an urban private clinic 40 miles from the border. Their findings were similar to ours. Our study provides more detailed data about this behavior and specifically addresses the issue of prescription medication purchased without a physician's advice. While this type of behavior is well known to practitioners in El Paso, it has never been quantified. The results of this study, even though the sample size is small, suggest that this type of behavior is widespread.

These data are important when one considers the large number of patients who are purchasing potentially dangerous medications without prescriptions in Mexico. One could argue that this behavior may be beneficial because it may help financially disadvantaged patients to obtain medications. Al-

Figure 1.—Some medications purchased in Mexico without a prescription are **(left to right from top to bottom)** Atisuril Plus (combination of probenecid and allopurinol), Artridol (combination of indomethacin, betamethasone, and methocarbamol), Mellitron (combination of metformin and chlorpropamide), Lincocin (lincomycin hydrochloride, injectable, purchased with a syringe), Beserol (antipyrine), and Neo-Melubrina (dipyrone).

Metformin is a biguanide similar to phenformin and is not available in the United States. Phenformin has been removed from the market in the United States by the US Food and Drug Administration. Antipyrine and dipyrone are pyrazolon derivatives that have been prohibited from use in the United States. They are analgesics that can cause fatal agranulocytosis.

though we have no data on hospital admissions in El Paso directly caused by complications from medications purchased in Mexico, our own experience suggests that serious medical problems do occur. For example, we have seen patients taking nonprescribed antibiotics who have severe allergic reactions.[7] One patient was transferred from our hospital for a bone marrow transplant after dipyrone ingestion that was associated with aplastic anemia. Recently, we admitted a 52-year-old man with acute renal failure and a large, infected buttocks ulcer. The patient had been self-administering intramuscular injections of steroids purchased in Juarez and also had been taking combination medications of phenylbutazone (Butazolidin) and steroids, indomethacin, and a combination of allopurinol and probenecid, all purchased over the counter in Juarez.

There are several limitations to the present study. Because it was designed as a pilot study, our sample size was small. A larger sample would provide useful confirmation. Although we suspect that the behavior we have described is prevalent in the El Paso population, our findings do not support this conclusion because our clinic population may not be representative of the El Paso population as a whole. For example, our sample was predominantly female, and our patients may have had more medical problems than the general population. Finally, we did not elicit specific information about the types of side effects experienced or the details surrounding admission to hospital.

Even with the above limitations, our results suggest that physicians along the US-Mexican border should be vigilant about the use of medications by their patients. A substantial number of medications in Mexico are either not approved for use in the United States (for example, phenformin) or contain

TABLE 4.—*Prescription Medication Purchased in Mexico*

Question	*Response*	N	*(%)*
Have you *ever* purchased medication in Juarez?	Yes	63	(81)
	No	15	(19)
Do you still purchase medication in Juarez?	Yes	50	(79)
	No	13	(21)
How often do you purchase medication in Juarez?	Once/mo or more	19	(32)
	Several times/yr	14	(23)
	Once/yr or less	3	(5)
	Other	24	(40)
Under what circumstances are the medications obtained?	Physician's prescription	17	(25)
	Clinic in Juarez	0	(0)
	Pharmacy in Juarez	51	(75)
	Other	0	(0)
Who recommended the medication to you?	Doctor	23	(28)
	Pharmacist	15	(19)
	Neighbor, friend, or relative	22	(27)
	Self	17	(21)
	Other	4	(5)
Why do you buy medicine in Juarez?	Less expensive	38	(49)
	Don't need prescription	16	(20)
	Medication not available in United States	3	(4)
	Convenience	8	(10)
	Better quality medicine	2	(3)
	Other	11	(14)
What types of medicines have you purchased in Juarez?	Blood pressure	11	(17)
	Diabetes	1	(2)
	Antibiotics	10	(16)
	Hormones	3	(5)
	Heart pills	0	(0)
	Arthritis	4	(6)
	Pain pills	2	(3)
	Other	32	(51)
Have you ever had side effects from these medications?	Yes	7	(11)
	No	57	(89)
Have you ever been hospitalized for side effects from medications purchased?	In Juarez	2	(3)
	In El Paso	0	(0)
	Never been hospitalized	61	(97)
If you compare medications purchased in Juarez with those purchased in El Paso	Those in Juarez are of higher quality	6	(10)
	Those in El Paso are of higher quality	8	(13)
	Equal quality	35	(57)
	No idea	12	(20)
Do you receive advice about side effects and dosage when you buy medicine in	Juarez only	0	(0)
	El Paso only	5	(8)
	Both	53	(88)
	Neither	2	(4)
When was the last time you purchased medications in Juarez?	Within the last wk	18	(28)
	Within the last mo	26	(41)
	Within the last 6 mo	8	(13)
	Within the last yr	6	(9)
	More than 1 yr ago	6	(9)
Do you know other people who buy medicine in Juarez?	Yes	52	(81)
	No	12	(19)

unusual combinations of medications that US physicians are not accustomed to using (for example, steroids in combination with nonsteroidal anti-inflammatory agents). Physicians practicing along the border may find it useful to have a copy of the *Diccionario de Especialidades Farmaceuticas,* the Mexican equivalent of the *Physicians' Desk Reference.*

From the results of this study, several conclusions can be made about the patients in our sample population:

- There was no substantial use of alternative health care, such as curanderos.
- Buying prescription medication in Mexico without a prescription is a common practice and is done frequently. The patient usually buys the medication on the advice of someone other than a physician.
- Patients buy medications in Mexico because they are less expensive there and a physician's prescription is not needed.
- Side effects do occur from this practice and may lead to a hospital stay.

Further study is needed to clarify the importance of this last finding.

Although the information from this study is most pertinent to physicians who practice at or near the border, it also is important for physicians in other areas of the United States because many Mexican-Americans migrate to areas distant from the border. In addition, tourists returning from a visit to Mexico may bring medications with them.[9]

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Conferences and Reviews

47-Year-Old Woman With Six-Week History of Lower Extremity Weakness and Eosinophilia

Moderators
PHILIP C. LEE, MD; CHRISTOPHER D. GOCKE, MD; *and* EDWARD D. HARRIS, Jr, MD

Discussants
MARK E. ANDERSON, MD, PhD; COLLEEN J. BERGIN, MD; JANET M. PRICE, MD; *and* JOHN W. LINDSEY, MD

This discussion was selected from the Department of Medicine Morbidity and Mortality Conference held at the Stanford University Medical Center, Stanford, California, on January 9, 1991. The editor of the conference is Philip C. Lee, MD, Chief Resident, Department of Medicine.

WE PRESENT A CASE *in which a 47-year-old woman had a six-week history of eosinophilia, bilateral weakness and paresthesias of the lower extremities, obstipation, and epigastric pain. Skin biopsies showed leukocytoclastic vasculitis, and a presumptive diagnosis of eosinophilic vasculitis was made. The patient's condition did not improve during a three-week course of high-dose corticosteroids. New weakness of the right hand, worsening weakness of the lower extremities, and bilateral numbness of the hands progressed rapidly. A massive intracranial hemorrhage occurred unexpectedly, and the patient died.*

MARK E. ANDERSON, MD, PhD*: A 47-year-old woman was transferred to Stanford University Medical Center from another hospital for evaluation and treatment of a hyper-eosinophilic syndrome and possible vasculitis.

History of Present Illness

The patient had a 20-year history of mild asthma but was otherwise well until three weeks before she was admitted to another hospital because of progressive bilateral pain and weakness in the lower extremities that notably limited her ability to walk. She also had abdominal pain. She was recently treated with quinine sulfate, and other routine medications included a β-agonist inhaler, a corticosteroid inhaler, and a theophylline preparation.

Physical examination revealed stable vital signs, diffuse abdominal tenderness without organomegaly or peritoneal signs, and bilateral weakness and painful paresthesias of the lower extremities (most prominent at the soles of the feet).

Pertinent laboratory studies included a leukocyte count of 29×10^9 per liter (29,000 per μl) with 0.76 (76%) eosinophils, erythrocyte sedimentation rate (ESR) 42 mm per hour, serum creatine kinase 56 units per liter, aldolase 9.8 units per liter (normal 1.2 to 7.6), alkaline phosphatase 608 units per liter, alanine aminotransferase (ALT) 140 units per liter, aspartate aminotransferase (AST) 146 units per liter, γ-glutamyl transferase 217 units per liter, and negative serologic tests for hepatitis A and B. Morning serum cortisol level was 718 nmol per liter (26 μg per dl) (normal 138 to 662 nmol per liter). Immunoglobulin measurements were as follows: IgA and IgM were within normal limits, IgG was 17.1 grams per liter (normal 5.4 to 14.8), and IgE was 0.9 mg per liter. Complement levels were within the normal range, and antinuclear antibodies, rheumatoid factor, and anti-*Trichinella* IgG were undetectable.

Bone marrow biopsy showed marked eosinophilic hyperplasia with no evidence of blasts, immature forms, or fibrosis. Nonblanching, raised petechial lesions developed on the patient's lower extremities, right arm, and neck that resolved spontaneously after four days. Multiple skin biopsies revealed leukocytoclastic vasculitis without a predominance of eosinophils. A presumptive diagnosis of eosinophilic vasculitis (Churg-Strauss syndrome) was made, and oral prednisone therapy was initiated at a dosage of 60 mg per day. Only minimal improvement of the pain in the lower extremities and abdomen occurred during the three weeks of hospitalization, although both the leukocytosis and eosinophilia decreased. The peripheral neuropathy did not progress, and the patient was discharged from the hospital.

One week later, the patient was readmitted because of worsening epigastric pain and obstipation. Pain and weakness of the lower extremities were unchanged. The patient was taking the medications given to her at the time of discharge: oral prednisone, 60 mg per day, carbamazepine, amitriptyline hydrochloride, sucralfate, and acetaminophen with codeine. Physical examination revealed no new abnormalities, and laboratory studies now showed a leukocyte count of 16×10^9 per liter (16,000 per μl) with 0.22 eosinophils, ESR 47 mm per hour, ALT 30 units per liter, and AST 37 units per liter. Imaging studies of the abdomen, consisting of examinations by plain x-ray film, ultrasonography, and computed tomography (CT), showed obstipation without evidence of free air or other pathologic abnormalities. Partial analgesia was obtained with narcotics, and the patient was transferred to Stanford University Medical Center.

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(Lee PC, Gocke CD, Harris ED, et al: 47-year-old woman with six-week history of lower extremity weakness and eosinophilia. West J Med 1992 May; 156: 517-522)

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
AST = aspartate aminotransferase
CNS = central nervous system
CT = computed tomography
ESR = erythrocyte sedimentation rate

Stanford Admission

On arrival, the patient reported the recent onset of progressive weakness of the right foot, bilateral numbness of the hands, and a 6.8-kg (15-lb) weight loss over the past eight weeks because of anorexia. She denied ingestion of tryptophan, raw meat or fish, or untreated water.

Past Medical History

The patient's medical history was significant for a 20-year history of asthma (without known sensitivity to salicylates), chronic sinusitis, and oophorectomy of the right ovary. She was gravida 4, para 3, and had had one spontaneous abortion. Medications at the time of transfer were prednisone, 60 mg per day, intravenous cimetidine, albuterol inhaler as needed, and buprenorphine hydrochloride (a parenteral opioid analgesic) as needed. She had no drug allergies. The patient had a ten pack-year history of cigarette smoking but had stopped 15 years ago. She admitted to occasional alcohol use but denied the use of illicit drugs. She was divorced and currently unemployed. Her father died of leukemia at 68 years of age, her mother died of an unknown malignant neoplasm at 68 years of age, and her grandson had asthma.

Physical Examination

The patient's temperature was 37.0°C (98.6°F), pulse 120 per minute, blood pressure 154/96 mm of mercury, and respiratory rate 16 per minute. She was thin and tearful. Her skin was remarkable for healed biopsy sites but was without other lesions. Examination of the head and neck showed mild bitemporal wasting, bilateral septal ulceration of the nares, and bilateral nonexudative perforations of the tympanic membranes. Small (<0.5 cm) firm lymph nodes were noted in the posterior cervical chain. Both lung fields were clear, and examination of the heart revealed a regular tachycardia with normal heart sounds and no jugular venous distension. The abdomen was flat with hyperactive bowel sounds. There was moderate to severe diffuse epigastric tenderness without rebound peritoneal signs, and no organomegaly was present. Rectal examination revealed no abnormalities, and a stool specimen was negative for occult blood. Pelvic examination yielded no abnormalities. No edema or cyanosis was present in the extremities, no tenderness of the muscles was apparent, and joints were without effusions.

The neurologic examination was limited because of pain and the effects of narcotic analgesia. A brief examination of her mental status and testing of cranial nerves showed no abnormalities. Power and tone in the upper extremities appeared normal, but power in the lower extremities was rated at 3 to 4 out of 5 in most muscle groups with 0/5 power in the dorsiflexors of the right ankle. Sensation to pinprick and light touch was diminished below the knees and over the distal palms and fingers bilaterally. Deep tendon reflexes were absent at the ankles but were otherwise present and symmetric. Plantar reflexes were downward.

Laboratory Data

A blood chemistry panel gave the following values: sodium 128 mmol per liter, potassium 4.3 mmol per liter, chloride 92 mmol per liter, bicarbonate 25 mmol per liter, blood urea nitrogen 2.1 mmol per liter (6 mg per dl), creatinine 44.2 μmol per liter (0.5 mg per dl), and glucose 6.3 mmol per liter (113 mg per dl). The total protein was 61 grams per liter, albumin 27 grams per liter, calcium 2.27 mmol per liter (9.1 mg per dl), phosphorus 1.03 mmol per liter (3.2 mg per dl), total bilirubin 3.4 μmol per liter (0.2 mg per dl), alkaline phosphatase 167 units per liter, ALT 25 units per liter, AST 34 units per liter, lactate dehydrogenase 425 units per liter, uric acid 150 μmol per liter (2.5 mg per dl), and cholesterol 3.78 mmol per liter (146 mg per dl).

The leukocyte count was 22.2×10^9 per liter (22,200 per μl) with 0.44 polymorphonuclear leukocytes, 0.01 band forms, 0.13 lymphocytes, 0.03 monocytes, and 0.37 eosinophils. The hematocrit was 0.33 (33.4%) with a mean corpuscular volume of 80 fl, and the platelet count was 570×10^9 per liter (570,000 per μl). Serum amylase was 34 units per liter, and the ESR was 34 mm per hour. Prothrombin time was 13.4 seconds, and activated partial thromboplastin time was 26.4 seconds. Urinalysis revealed a specific gravity of 1.013, pH greater than 8, 1 to 5 leukocytes per high-power field with 0.01 urinary eosinophils but no erythrocytes or casts. An electrocardiogram showed sinus rhythm at a rate of 98 per minute with no acute changes. The chest radiograph showed normal heart size and clear lungs. A plain roentgenogram of the abdomen also showed no abnormalities, and x-ray films of the sinuses revealed slight thickening in the right frontal and maxillary sinuses without the presence of air-fluid levels.

Hospital Course

On the first hospital day, prednisone therapy was continued at a dosage of 60 mg per day. The patient had persistent pain in the lower extremities and abdomen. Neurologic findings were unchanged, and examination of the stool yielded no ova or parasites.

On the second day, the abdominal pain lessened somewhat, but a new right wrist-drop developed, and numbness of both hands was reported to be worse. Biopsy of the nasal mucosa showed numerous extravascular eosinophils with no evidence of vasculitis or granulomas. Blood pressures ranged between 140/80 and 180/100 mm of mercury.

On the third hospital day, it was decided that the patient should receive treatment with cyclophosphamide. Before the drug could be administered, however, the patient was discovered to be unresponsive and apneic with fixed and dilated pupils. She was intubated with an oral endotracheal tube, and an emergent CT scan of the head revealed massive subarachnoid and intraventricular hemorrhage. The patient was transferred to the intensive care unit and treated with mannitol and hyperventilation, and a ventriculostomy was done.

On the fourth hospital day, there was no significant change in the patient's clinical status. Neurologic examination showed no change, the patient had no spontaneous respirations, and she was determined to be brain dead by established criteria. After discussion with the family, the patient was taken off mechanical ventilation and progressed rapidly to asystole.

Radiologic Discussion

COLLEEN J. BERGIN, MD*: Figure 1 shows CT scans of the head obtained without intravascular contrast material on the third hospital day. The images showed the presence of high-density material within the ventricles suggesting intraventricular hemorrhage. Blood was also noted in all the basal cisterns and within the sulci and interhemispheric fissures, signifying a large subarachnoid hemorrhage. There was no evidence of intraparenchymal hemorrhage. Generally, this pattern is suggestive of a massive subarachnoid hemorrhage with retrograde reflux of blood into the ventricles. However, it is also consistent with a primary intraventricular hemorrhage with subsequent spread into the subarachnoid space.

The most common cause of massive subarachnoid hemorrhage is a saccular aneurysm, but there was no evidence of this on the CT scan. Less commonly, this type of hemorrhage may result from an arteriovenous malformation or tumor. Although cerebral vasculitis may cause an intraparenchymal hemorrhage, primary hemorrhage into the ventricles and subarachnoid space as a result of this disorder would be extremely uncommon. The initial site of intracranial bleeding could not be ascertained from this CT scan.

Clinical Discussion

EDWARD D. HARRIS, JR, MD†: Did the patient have Churg-Strauss syndrome?

JANET M. PRICE, MD‡: This case illustrates some of the features unique to the Churg-Strauss syndrome, a disorder characterized by hypereosinophilia, systemic vasculitis, and bronchial asthma. Also known as allergic granulomatosis and angiitis, this syndrome was first described in the literature in 1951.[1] Three phases have been described, all of which were observed in this patient.[2] The initial prodromal phase usually consists of an allergic disease that may persist for several years. During the second phase, peripheral eosinophilia with tissue eosinophil infiltrates appears. The extremely high peripheral eosinophil counts present in this patient are characteristic, and examples of extravascular eosinophilia include eosinophilic pneumonia and gastroenteritis. Finally, the third phase is characterized by systemic vasculitis, usually involving two or more extrapulmonary organ systems. In this case, the patient had a long history of asthma that developed in adulthood. She had transient apical infiltrates on the chest radiograph about the time she was admitted to the hospital with eosinophilia, and she may well have had pulmonary involvement. Her skin and peripheral nervous system were clearly involved, and there was strong clinical suspicion of involvement of the gastrointestinal and central nervous systems (CNS) as well.

The American College of Rheumatology has recently defined six criteria that distinguish the Churg-Strauss syndrome from other forms of vasculitis.[3] These are the presence of asthma, eosinophilia of more than 10% on the differential leukocyte count, a mononeuropathy (including multiplex) or polyneuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormality, and a biopsy specimen containing extravascular eosinophils. All six of these findings were present in this patient. It is important to note that

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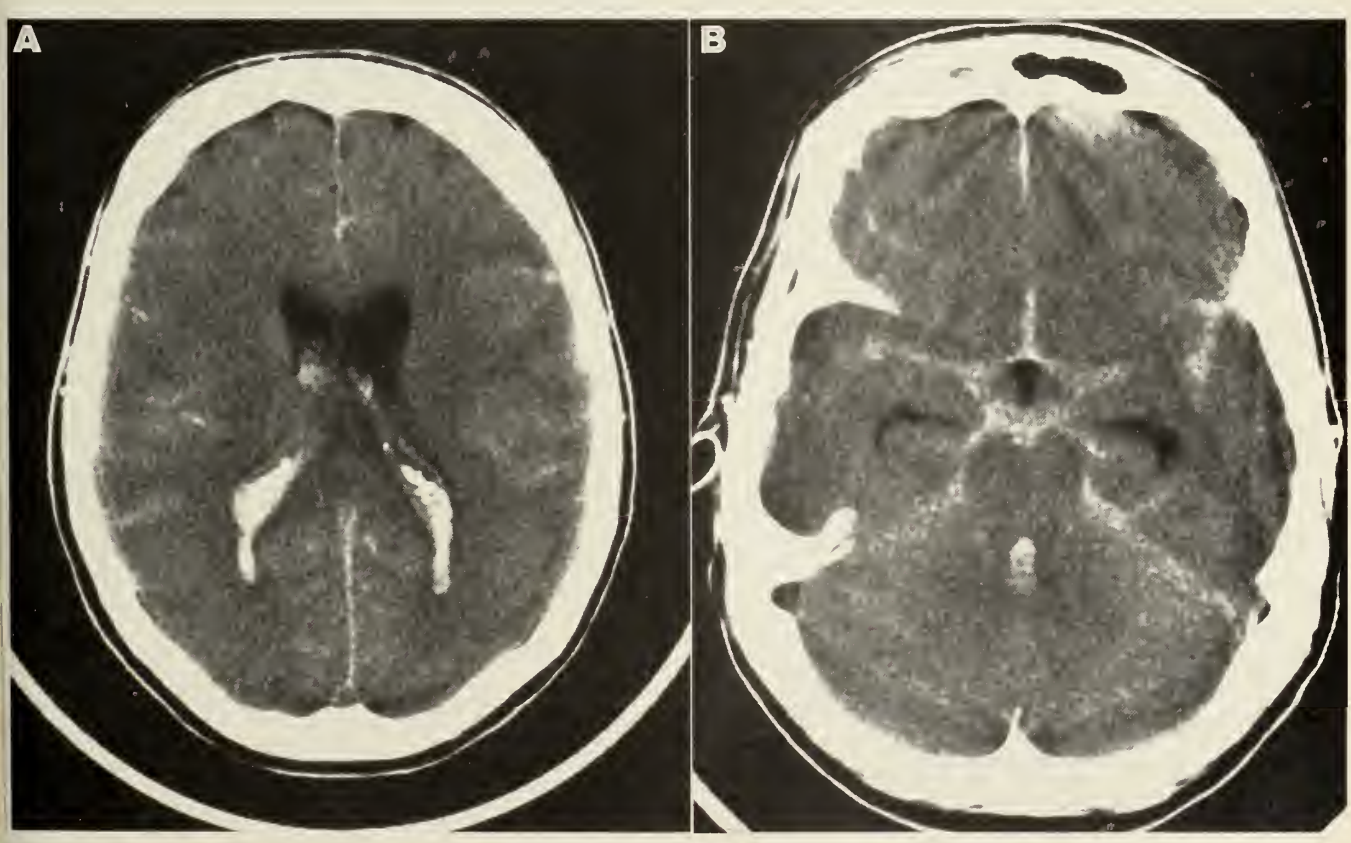

Figure 1.—Computed tomographic scans of the head without intravascular contrast material show massive intraventricular and subarachnoid hemorrhage. **A,** Scan shows blood (high-density material) in the lateral ventricles and sulci bilaterally. The choroid plexus was noted to be calcified. **B,** This view shows blood in the fourth ventricle and in all cisternal spaces.

the intravascular and extravascular granulomatous changes described by Churg and Strauss in their original report[1] are not part of the current American College of Rheumatology criteria.

DR HARRIS: Should the patient have received cyclophosphamide therapy?

DR PRICE: Of all the systemic vasculitides, the Churg-Strauss syndrome is one of the most steroid-responsive.[2] Characteristically, there is a dramatic fall in the peripheral eosinophil count within days of the initiation of corticosteroid therapy. Symptomatic improvement closely follows, with the exception of the neurologic changes, which typically take months to improve. Unfortunately, clinical relapse is common, even with continued steroid therapy, and in many cases the disease may progress as a smoldering vasculitis.

If the eosinophil count fails to return to the normal range and the patient does not demonstrate a clinical remission, then cyclophosphamide therapy should be instituted. An initial response followed by clinical relapse is also an indication for cyclophosphamide therapy. In this case, the patient had clear progression of neuropathic manifestations with a new right wrist-drop, and cyclophosphamide therapy was recommended. Unfortunately, she had a catastrophic CNS event before the drug could be administered.

Azathioprine has also been used to treat refractory or relapsing cases of Churg-Strauss syndrome. In a review of the literature, we found no clinical trials or series of cases that directly compare the efficacy of cyclophosphamide and azathioprine in this disease. At least one author advocates the use of cyclophosphamide early in the course of acutely ill patients and the use of azathioprine as a steroid-sparing or maintenance drug in refractory cases.[2]

DR HARRIS: How were the patient's neurologic symptoms related to her having Churg-Strauss syndrome?

JOHN W. LINDSEY, MD*: This patient had a multisystem illness with two prominent neurologic manifestations: a painful polyneuropathy and an intracranial hemorrhage. The neuropathy showed clinical features of both a mononeuritis multiplex and a diffuse sensorimotor polyneuropathy. This is typical for what has been reported for the Churg-Strauss syndrome. Churg and Strauss, in their original report of 13 cases,[1] noted nine patients with neuropathy with "variable motor, sensory, and trophic disturbances." In a series of 30 cases from the Mayo Clinic,[4] 19 had a neuropathy, usually a mononeuritis multiplex. Lanham and associates, in their series of 16 cases and an extensive review of the literature, noted mononeuritis multiplex in 12 of their patients, with the neuropathy being the most prominent clinical finding in 6.[2] About two thirds of the patients in their review of the literature had mononeuritis multiplex. The severe pain experi-

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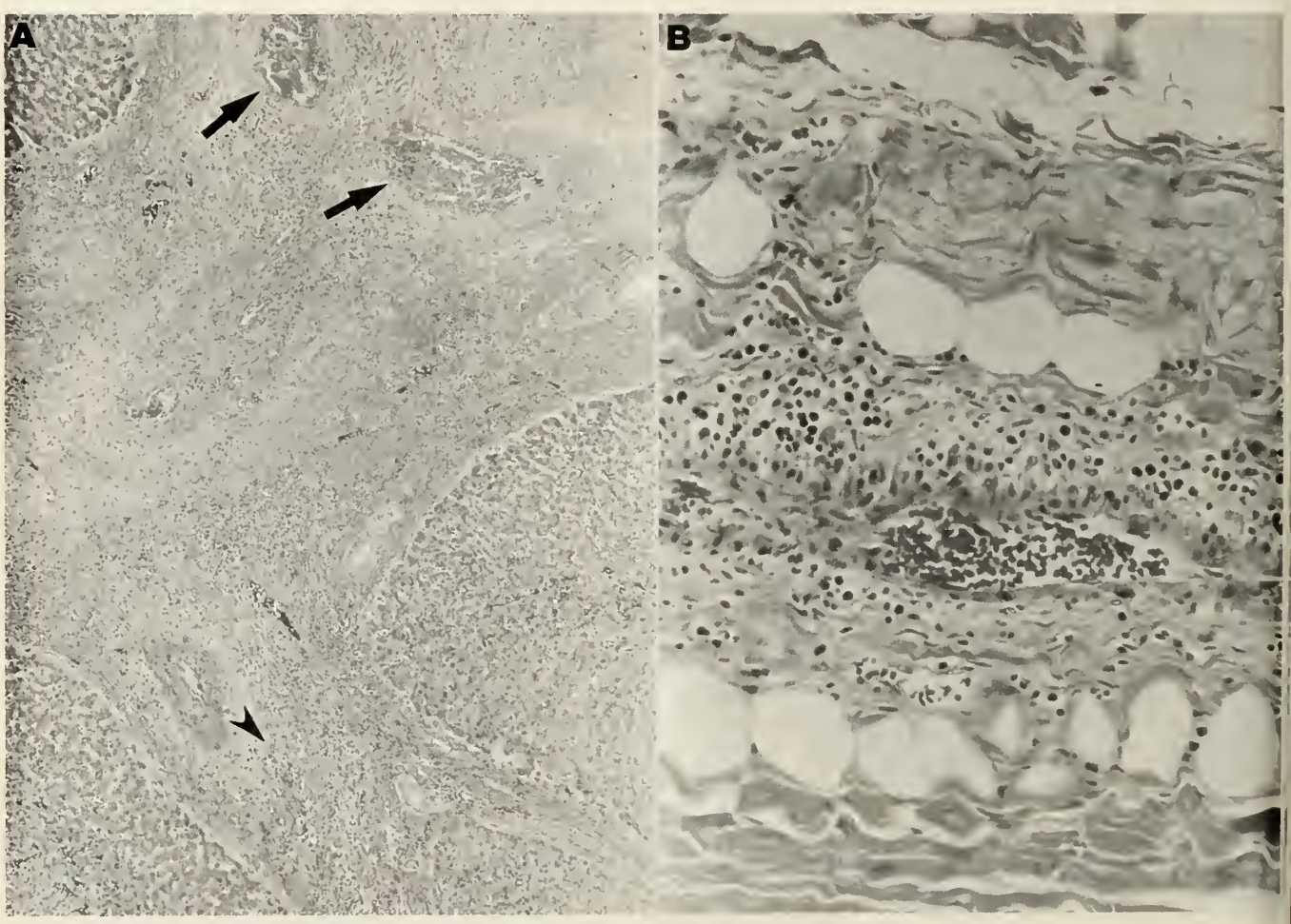

Figure 2.—Histologic slides of tissue obtained at autopsy show vasculitis involving liver and peripheral nerve. **A,** Note in the hepatic portal zone recanalization of thrombosed vessels **(arrow)** and active vasculitis **(arrowhead)** (hematoxylin and eosin stain, original magnification × 30). **B,** A random peripheral nerve specimen shows an adjacent perivascular eosinophilic infiltrate (hematoxylin and eosin stain, original magnification × 125).

enced by this patient does not appear to be typical but has been reported.[5]

Involvement of the CNS in the Churg-Strauss syndrome was originally thought to be as common as the presence of neuropathy, but it has been described less frequently in more recent series. Churg and Strauss reported CNS involvement in 8 of their 13 patients.[1] One had a subarachnoid hemorrhage, and two had cerebral hemorrhage. The symptoms were not specified in the other five, and postmortem microscopic findings in brain tissue were not reported. In contrast to this high incidence of CNS symptoms, none of the 30 patients in the Mayo Clinic series were reported to have CNS symptoms,[4] and none of the 15 deaths were due to intracranial hemorrhage. Lanham and colleagues reported unspecified CNS involvement in 4 of their 16 patients and in 27% of the cases in their literature review.[2]

Intracranial hemorrhage is perhaps the best known CNS complication of patients with Churg-Strauss syndrome. It may be related to CNS vasculitis or hypertension,[2] but clear pathologic documentation of its cause is lacking. Review of the literature yielded a case report that describes the presence of an eosinophilic CNS vasculitis in a hypertensive patient who died of a massive cerebral hemorrhage.[6] The authors suggested that the patient had periarteritis nodosa, but in retrospect her clinicopathologic syndrome seems more consistent with the Churg-Strauss syndrome based on recent criteria.[3,7] Another case report of allergic granulomatous angiitis associated with subarachnoid hemorrhage[8] is of interest because microscopic examination of a resected anterior cerebral aneurysm revealed necrotizing angiitis with infiltration of eosinophils. It is not clear, however, if this patient did indeed have the Churg-Strauss syndrome. If the pathologic findings of our patient demonstrate a CNS vasculitic process, then this will confirm the previously suspected link between CNS vasculitis and intracranial hemorrhage in patients with the Churg-Strauss syndrome.

Pathologic Findings

CHRISTOPHER D. GOCKE, MD*: Examination at autopsy revealed a systemic necrotizing vasculitis involving numerous organs. Although no gross lesions were evident, the liver, heart, spleen, gastrointestinal tract, skeletal muscle, and peripheral nerves all contained affected blood vessels. The vasculitis was patchy and varied in intensity: although cutaneous and renal involvement was minimal, some severely affected vessels in the liver appeared to have undergone recanalization (Figure 2A). The inflammatory process was characterized by a mixed infiltrate rich in eosinophils and involved arterioles and small to medium-sized muscular arteries, sparing the venous system. The vasculitis was often transmural, and fibrinoid necrosis was frequently found. Numerous eosino-

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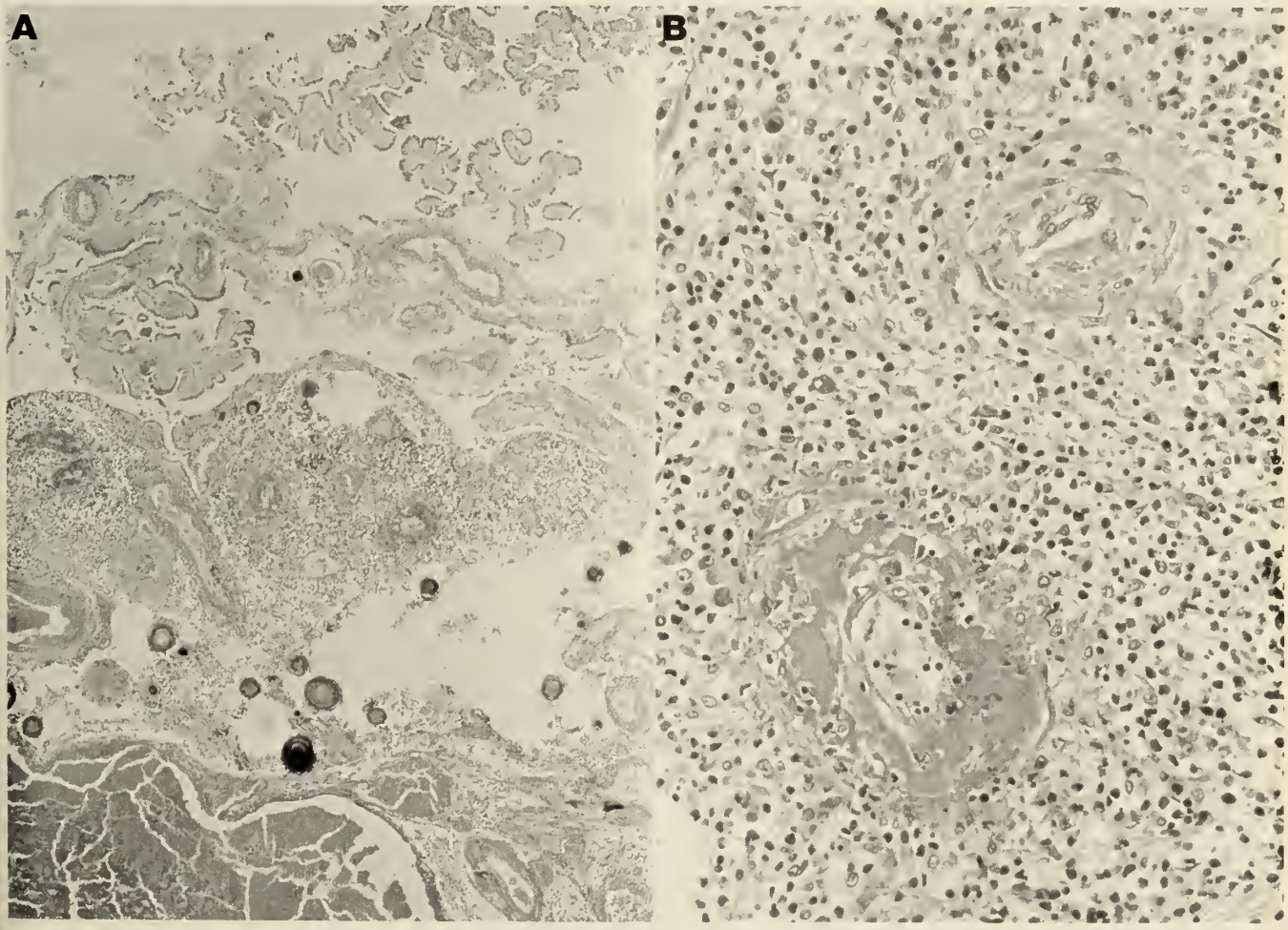

Figure 3.—Histologic slides of tissue obtained at autopsy show vasculitis in the central nervous system involving the choroid plexus. A, Note the florid eosinophilic vasculitis of the choroid plexus (hematoxylin and eosin stain, original magnification × 30). B, Transmural inflammation (predominantly composed of eosinophils) with fibrinoid necrosis is shown (hematoxylin and eosin stain, original magnification × 125).

phils were present in perivascular soft tissues, and Figure 2B shows such involvement of a peripheral nerve. The eosinophilia was particularly striking in the bone marrow, which was of normal cellularity but contained approximately 50% eosinophils. The nasal sinus mucosa showed acute and chronic inflammation without evidence of vasculitis, and only mild eosinophilic capillaritis of the pulmonary vessels was present. No granulomas were present, and histologic examination revealed no microorganisms.

A large recent subarachnoid hemorrhage covered the base of the brain as well as both cerebral hemispheres. The ventricular system was dilated and filled with blood. Except for microscopic dissection of the hemorrhage into the basal ganglia from the ventricular system, the parenchyma and subarachnoid tissue of both brain and spinal cord showed no abnormalities. A striking necrotizing eosinophilic vasculitis involved the vessels of the choroid plexus with surrounding hemorrhage (Figures 3A and B). Similar lesions were noted in vessels of spinal epidural fat but were not seen in either gray or white matter. There were no aneurysms in either cerebral or visceral blood vessels.

The patient's death can be attributed to vasculitis of the choroid plexus with primary hemorrhage into the ventricles and subsequent propagation into the subarachnoid space. Primary intraventricular hemorrhage is extremely uncommon, and lesions of the choroid plexus as a cause of bleeding are even more rare.[9] Although vasculitis involving the CNS has not been well documented in patients with Churg-Strauss syndrome, intracranial hemorrhage as a cause of death has been clearly associated with this disorder.[1] The role of hypertension as one of the factors associated with intracranial hemorrhage in these patients has also not been well defined. Similarly, the incidence and epidemiology of choroid plexus vasculitis are completely unknown; the paucity of reports describing this disorder in the literature may well result from the fact that microscopic analysis of choroid plexus tissue is not done routinely in the majority of postmortem examinations. This is the first documented case of choroid plexus vasculitis in a patient with Churg-Strauss syndrome resulting in death.

As the histopathologic criteria for classifying the systemic vasculitides are being established,[7] three features have been suggested as characteristic of the Churg-Strauss syndrome: eosinophilic granulomas, soft tissue eosinophilia, and a systemic vasculitis exhibiting fibrinoid necrosis.[10] The confluence of all three features in patients with Churg-Strauss syndrome is uncommon, occurring in only 13% to 24% of a large series of patients.[2] Eosinophilic granulomas (as initially described by Churg and Strauss[1]) appear to be a helpful marker for the syndrome when present but are by no means specific or necessary for the diagnosis. As many as 60% of patients with Churg-Strauss syndrome lack eosinophilic granulomas at autopsy,[2] and they were absent in our patient. Both soft tissue eosinophilia and systemic vasculitis were seen in our patient, confirming the diagnosis of Churg-Strauss syndrome.

Final Anatomic Diagnoses

- Necrotizing systemic vasculitis with eosinophilia (Churg-Strauss syndrome).
- Choroid plexus vasculitis with massive intraventricular and subarachnoid hemorrhage.

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Tumors of the Kidney, Ureter, and Bladder

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Neoplastic processes involving the kidneys, the ureters, or the bladder account for 10% of all tumors in men and 4% of all tumors in women.[1]* Tumors of these organs represent a broad histologic range and vary widely in their clinical behavior. Despite this diversity, a common presenting feature of these lesions is either gross or microscopic hematuria. More than 85% of patients with uroepithelial neoplasia and 59% of patients with renal parenchymal tumors have this associated finding.[2,3] For this reason, a clear understanding of the evaluation of patients presenting with hematuria is germane to the discussion of tumors of these organs.

Evaluation of Microscopic Hematuria

Up to 13% of asymptomatic adult patients may present with microscopic hematuria.[4] Table 1 lists an abbreviated differential diagnosis for this common finding.[5] It is a clinician's responsibility to distinguish those patients with benign conditions from those with malignant urinary tract diseases. Because tumors of the urinary tract primarily affect the adult population, the following discussion will focus on this group of patients.

As with any disease, a thorough history and physical examination constitute the framework for further evaluation. Clearly the differential diagnosis in an elderly man with flank pain and a palpable flank mass will be different from that of a sexually active woman who presents with urinary frequency and urgency, despite the fact that both may have microscopic hematuria. Historical evaluation must include any record of urologic diseases and manipulation as well as any background of urinary tract infections, calculus disease, or previous neoplasms. A history of local or constitutional symptoms as well as previous traumatic injury must be sought. A complete physical examination with special attention to the abdomen, flanks, and external genitalia in men and a pelvic examination in women is essential.

The urinalysis should be repeated in all patients seen for microscopic hematuria. In the microscopic evaluation of the centrifuged urinary sediment, the presence of more than 1 to 3 erythrocytes per high-power field is considered an abnormal result.[6,7] The presence or absence of associated pyuria, bacteriuria, or proteinuria may be important in establishing the cause of hematuria. Red blood cell morphology may aid in distinguishing glomerular hematuria from that of more distant sites.[8,9] All patients with microscopic hematuria must have a urine culture.

Failure to establish a clear diagnosis at this point in the evaluation indicates the need for further study. The subsequent workup should include excretory urography or renal ultrasonography in combination with cystoscopy. Renal ultrasonography in combination with cystoscopy may be the most cost-effective strategy for evaluating asymptomatic microscopic hematuria, with a sensitivity and specificity identical to strategies that include excretory urography.[10] We prefer to do imaging studies of the upper urinary tract before cystoscopy because findings in the upper tract may influence the nature and extent of subsequent endoscopic evaluation. Filling defects in the upper urinary tract may warrant retrograde pyelography, upper tract cytology, or ureteropyeloscopy alone or in combination as part of the diagnostic evaluation.

Evaluation of Gross Hematuria

The discussion has so far been limited to asymptomatic patients who present with microscopic hematuria. In addition to the history, physical examination, urinalysis, and urine culture, all patients with gross hematuria or symptoms attributable to the urinary tract in association with microhematuria warrant excretory urography and cystoscopy. Only rarely will these diagnostic studies fail to establish a clear diagnosis in patients with gross hematuria. Historically, these unusual patients required interval evaluation with excretory urography and cystoscopy to preclude an occult malignant neoplasm. Recent advances in fiberoptic instrumentation, however, now enable urologists to visualize the upper urinary tract directly. Flexible ureteropyeloscopy is now established as an important diagnostic study in patients with otherwise unexplained gross hematuria.[11,12]

Patients With a Renal Mass

The diagnostic studies just outlined will identify a subset of patients with renal masses. In addition to patients identified as having hematuria, an increasing number of incidental renal masses are being discovered in patients undergoing diagnostic studies for other reasons. In the past, surgical exploration was often necessary to define the nature of a renal mass. Rapid advances in cross-sectional imaging techniques now enable the establishment of the diagnosis before a surgical procedure in more than 90% of all cases. This diagnosis often obviates the need for surgical intervention.

An algorithm for evaluating a patient with a renal mass is shown in Figure 1. The specific decision path depends on whether or not a renal mass is identified initially by ultrasonography or excretory urography. Computed tomography (CT) is warranted in patients whose excretory urogram shows a contrast-enhancing renal mass.

*See also "Tumors of the Urinary Tract," by Marc B. Garnick, MD, elsewhere in this issue (page 556).

(See WA, Williams RD: Tumors of the kidney, ureter, and bladder. West J Med 1992 May; 156:523-534)

From the Department of Urology, University of Iowa Hospitals and Clinics, Iowa City.

This work is an update to the Cecil Textbook of Medicine, 19th edition, WB Saunders Co, Philadelphia, Pennsylvania.

Reprints not available.

ABBREVIATIONS USED IN TEXT

BCG = bacillus Calmette-Guérin
CT = computed tomography
MRI = magnetic resonance imaging
PTH = parathyroid hormone
RCC = renal cell carcinoma

For nonenhancing masses identified by excretory urography, it is vital to differentiate solid from cystic lesions. Ultrasonography has proved highly sensitive—95% accurate—in this regard and is therefore the next diagnostic study. Lesions that fulfill the ultrasonographic criteria of simple cysts—peripheral location, smooth thin wall, absence of internal echoes, and posterior wall enhancement—require no further evaluation. Complex renal cysts or solid masses require further workup as indicated in the algorithm. On occasion, renal ultrasonography fails to identify a mass suspected on excretory urography. In these cases a dimercaptosuccinic acid (DMSA) isotope scan of the renal cortex or renal CT scan may aid in the evaluation.

A patient in whom the ultrasound study, obtained either initially or after excretory urography, demonstrates a solid or complex renal mass requires an abdominal CT scan. Contrast enhancement of a renal mass is an important feature of neoplasia. Sections should therefore be obtained through the area of interest both before and after the administration of intravenous contrast (Figures 2 and 3). Other CT findings may provide clues to the diagnosis. Angiomyolipomas are characterized as inhomogeneous masses with areas of low-density fat. Renal oncocytomas may demonstrate a central stellate scar.

In a patient with a suspected neoplasm, an abdominal CT scan also provides important staging information. The local extent of the lesion, status of the contralateral kidney, nodal enlargement, renal vein or vena caval involvement, and other sites of intra-abdominal metastasis may be defined using this technique. On rare occasions, additional imaging techniques may be necessary. In indeterminate cases (5% to 8%), renal arteriography, needle aspiration cytology, or cyst puncture may be needed to establish the diagnosis.

The role of magnetic resonance imaging (MRI) in evaluating renal mass lesions has yet to be defined. Early experience suggests that the ability of MRI to acquire primary data from multiple planes may be useful in local tumor staging—defining pararenal fat, para-aortic nodal and adjacent organ extension, and intravascular tumor thrombi (Figure 4).[13,14] The development of paramagnetic agents capable of contrast-like enhancement may expand the usefulness of MRI.[15]

Despite the impressive diagnostic armamentarium now available, it is occasionally impossible to establish a diagnosis. In these cases a decision between observation and surgical exploration must be made based on an assessment of the risks to an individual patient.

Benign Renal Tumors

Table 2 lists common renal tumors.[16] Any histologic component of the kidneys may be associated with benign neoplastic growth. Often the distinction between benign and malignant renal processes is based more on biologic behavior in a given patient than on histologic type. The best example of this is the so-called renal adenoma.

Renal Adenomas

Renal adenomas are the most common benign solid parenchymal lesions. By definition they are less than 3 cm and are often histologically indistinguishable from renal cell carcinoma (RCC). They tend to occur in circumstances similar to RCC in that they occur most frequently in patients older than 40 and have a 3:1 male-to-female ratio.[17(p435)] These lesions have been designated benign by some investigators based on the benign clinical course following surgical re-

TABLE 1.—*Causes of Hematuria**

Hematologic
Coagulopathy
Anticoagulation
Sickle cell anemia and trait
Sickle cell-thalassemia
Sickle cell-hemoglobin C disease

Renal (glomerular)
Acute proliferative glomerulonephritis (GN) (poststreptococcal GN)
Primary mesangiopathic GN (Berger's disease and other nonsystemic focal proliferative GN)
Focal proliferative GN associated with systemic disease (Henoch-Schönlein purpura, vasculitis)
Rapidly progressive GN (any cause)
Lupus nephritis
Membranoproliferative GN
Alport's syndrome
Benign familial hematuria
Any other glomerular lesion

Renal (nonglomerular)
Nephrosclerosis secondary to hypertension
Renal infarct
Renal vein thrombosis (infants)
Tuberculosis
Pyelonephritis
Polycystic disease
Medullary sponge kidney
Interstitial nephritis (drug allergy, infection)
Tumors
Vascular malformations
Trauma
Papillary necrosis
Cortical necrosis
Perirenal hematoma (infants)

Postrenal
Stones
Periureteritis secondary to extraurinary pathology
Tumors of lower urinary tract
Cystitis (schistosomal, bacterial, viral, drug-induced, radiation, idiopathic)
Prostatitis
Epididymitis
Meatal ulceration (circumcised boys)
Urethral stenosis
Foreign bodies of bladder or urethra (including Foley catheter)
Strenuous exercise
Urethritis
Phimosis
Benign prostatic hypertrophy
Obstruction
Vascular malformations
Endometriosis
Vesicoureteral reflux

False
Red diaper syndrome
Vaginal bleeding
Bleeding circumcision
Factitious
Pigmenturia
- Porphyria
- Hemoglobinuria
- Myoglobinuria
- Food—beets, blackberries, rhubarb
- Drugs

*Adapted from Abuelo.[5]

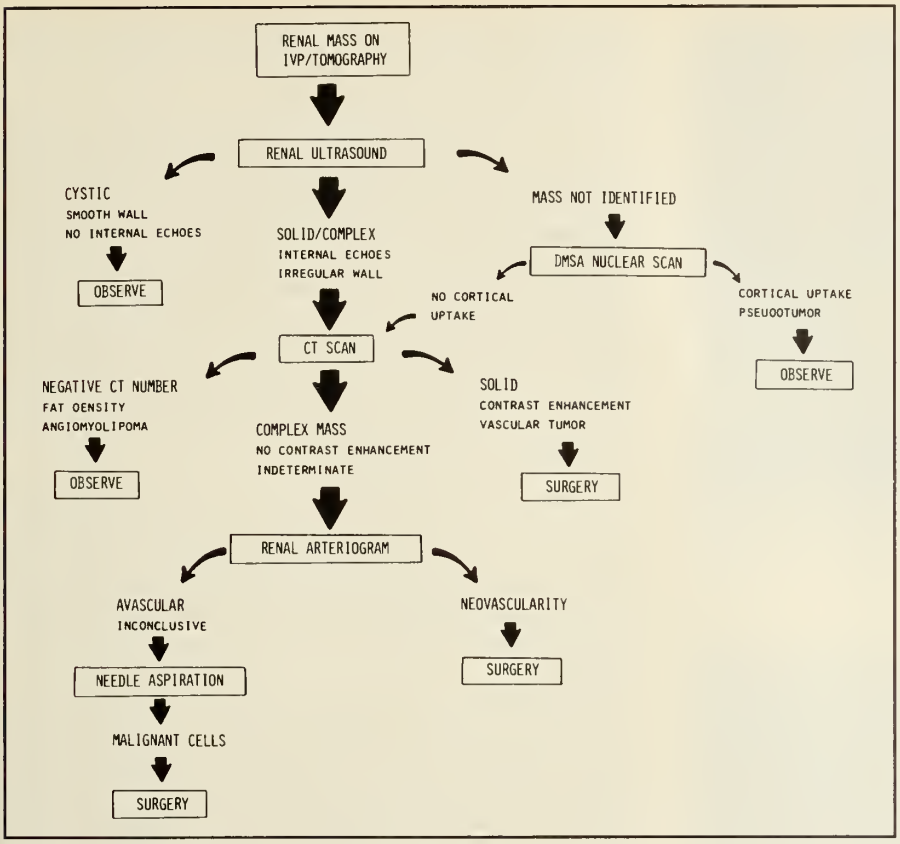

Figure 1.—An algorithm is presented for the evaluation of patients with suspected renal masses. CT = computed tomography, DMSA = dimercaptosuccinic acid, IVP = intravenous pyelogram

moval of the lesions. Renal adenomas have been reported to metastasize, however, and they should probably be considered to represent an early stage of RCC.[18] For this reason, current recommendations are for surgical removal. Although radical nephrectomy is usually advocated, trials of subtotal nephrectomy in highly selected patients have met with good results.[19]

Oncocytoma

Renal oncocytoma, a subtype of adenoma accounting for 5% to 7% of renal tumors, is indistinguishable preoperatively from renal adenoma and RCC. Classically, these lesions have a spoke-wheel pattern on the angiogram. This, however, is not sufficient to exclude a malignant lesion, and treatment continues to be radical nephrectomy. Renal oncocytomas have a pale brown appearance and histologically contain cells with an abundant acidophilic cytoplasm.

Angiomyolipoma

Hamartoma-angiomyolipoma is most often observed in conjunction with a diagnosis of tuberous sclerosis (adenoma sebaceum, epilepsy, and mental retardation).[20] These lesions tend to be multiple, synchronous, or metachronous and are commonly bilateral. As the name implies, they contain vas-

TABLE 2.—*Classificatian of Renal Neaplasms**

Benign
Adenoma
Oncocytoma
Angiomyolipoma/hamartoma
Fibroma
Leiomyoma
Lipoma
Hemangioma
Juxtaglomerular tumor

Primary malignant
Renal cell carcinoma
Urothelial—renal collecting system and pelvis—transitional cell, squamous cell, and adenocarcinoma
Sarcoma

Secondary malignant
Adrenal carcinoma
Retroperitoneal sarcoma, pancreas, colon (direct extension)
Lung, stomach, breast, prostate (hematogenous metastases)
Hematologic tumors—lymphoma, leukemia
Multiple myeloma (primary or metastatic)

*Adapted from Williams.[16]

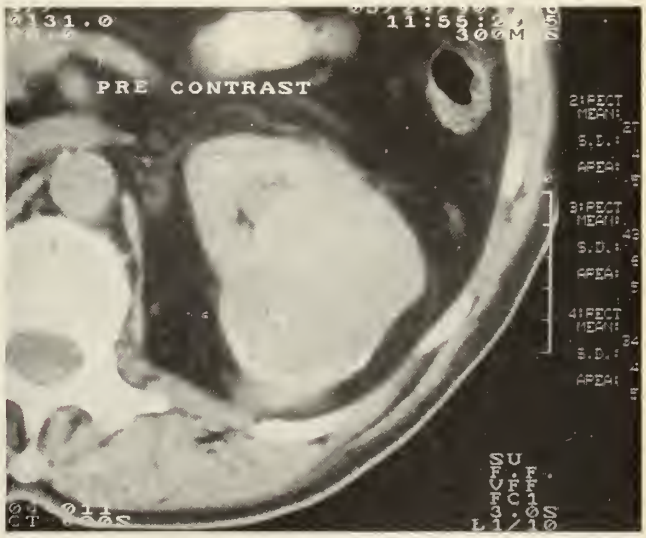

Figure 2.—Noncontrast-computed tomographic scan through a left renal mass lesion (O_2 and O_3) is shown.

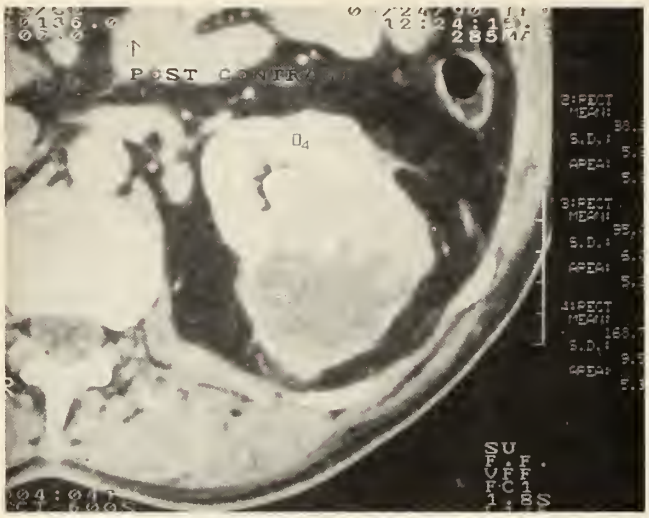

Figure 3.—A contrast-enhanced computed tomographic scan through the identical plane seen in Figure 2 shows the areas of contrast enhancement and tissue inhomogeneity characteristic of neovascularity and necrosis within the tumor (O_2).

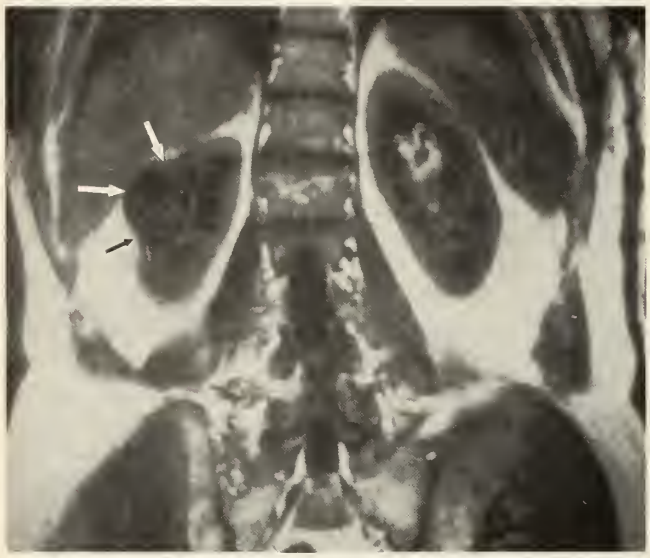

Figure 4.—A coronal T1-weighted magnetic resonance image through the right kidney shows a clear plane between the right renal mass lesion (arrows) and the liver.

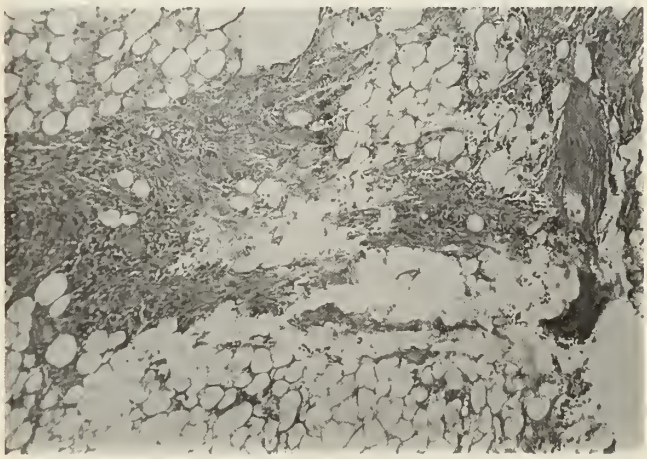

Figure 5.—Histologic examination of a renal angiomyolipoma shows prominent vascular and fat components (hematoxylin and eosin; original magnification × 63).

cular, adipose, and smooth muscle elements. Their vascularity may account for their common presentation with retroperitoneal hemorrhage (Figure 5).

In contrast to other neoplasms, angiomyolipoma can be diagnosed with a high degree of certainty using CT and ultrasonography. The fat content of the tumor, manifested as low-density areas on CT or highly echoic regions on ultrasound, may enable establishment of the diagnosis. Asymptomatic patients with these classic findings and small (< 5 cm) tumors, particularly associated with tuberous sclerosis, do not require a surgical procedure and have an excellent prognosis without treatment. The diagnosis may be more difficult to establish in patients without classic radiographic changes. When doubt exists, they should be surgically removed.

Acquired Renal Cystic Disease

Patients with end-stage renal disease are at risk of developing multiple bilateral cysts in the renal cortex as a direct function of the duration of their renal failure.[21] As many as two thirds of the patients on dialysis for four or more years have findings characteristic of this process.[22] The risk of cyst development appears to be independent of the type of dialysis.[23]

Of greatest concern in patients with acquired renal cysts is the risk of developing renal carcinoma. As many as 4% of patients with end-stage renal disease and acquired cystic disease have been noted to develop RCC.[24] As many as 9% of patients on long-term dialysis have been reported to have benign or malignant renal growths, an approximately 30-fold increase compared with azotemic patients not on dialysis.[25]

The true incidence of RCC in patients with acquired cystic disease is still undefined, but there does appear to be some increase relative to the normal population. For this reason we advocate baseline and interval ultrasonographic follow-up of all patients on dialysis. Our algorithm for the follow-up and management of such patients is shown in Figure 6.[26] Patients

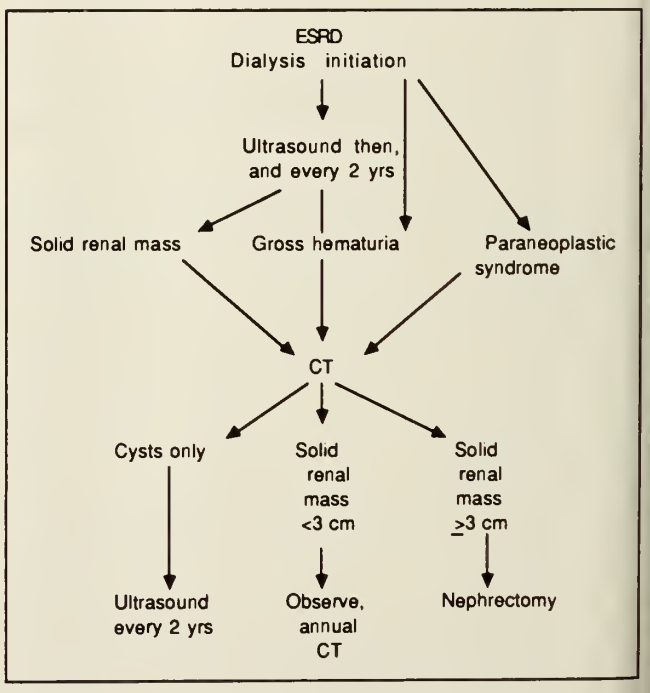

Figure 6.—An algorithm is presented for the follow-up of patients at risk for acquired renal cystic disease (from Fallon and Williams[26]). CT = computed tomography, ESRD = end-stage renal disease

with ultrasonographically detected solid renal masses or hematuria should undergo the evaluation described previously for these findings.

Xanthogranulomatous Pyelonephritis

Because of its tendency to mimic neoplastic processes, xanthogranulomatous pyelonephritis has been termed the great imitator.[27] Histologically, this is a destructive renal process resulting from chronic infection and inflammation. Normal renal parenchyma is replaced by inflammatory cells, histiocytes, and macrophages. This diagnosis should be suspected in patients with a history of chronic urinary tract infection (particularly with *Proteus* species) and persistent pyuria or bacteriuria, particularly in association with calculous disease of the kidney. Treatment consists of partial or total nephrectomy, depending on the extent of renal involvement.

Miscellaneous Benign Neoplasms

A variety of other benign renal tumors include the following: fibroma, a renal medullary fibrous mass most commonly found in female patients; lipoma, an adipose deposition within or around the kidney, often perihilar or within the renal sinus; leiomyoma, a not uncommon retroperitoneal tumor that may arise from the renal capsule or renal vessels; and hemangioma, a lesion that occasionally accounts for hematuria with an elusive cause. It is often difficult to establish a diagnosis of these less commonly encountered benign renal tumors. When they are accompanied by symptoms or produce a renal mass with caliceal distortion, the final diagnosis is generally made by a pathologist after the kidney is removed.

Malignant Renal Neoplasms

Renal Cell Carcinoma

Renal cell carcinoma is the most common renal carcinoma in adults, accounting for 3% of all cancers and approximately 9,000 deaths per year in the United States. The tumor is also called renal adenocarcinoma, Grawitz's tumor, hypernephroma, and nephrocarcinoma, although renal cell carcinoma has become a universally accepted designation. Renal cell carcinoma appears to arise from cells of the proximal convoluted tubule. Risk factors include cigarette smoking, obesity, and male sex (ratio of 2 or 3:1).[28] Persons with HLA antigen types Bw44 and DR8 may be more prone to have renal cancer, and evidence suggests that oncogenes localized to the short arm of chromosome 3 may have etiologic implications.[29,30] Renal cell carcinoma is occasionally familial and is more common in patients with von Hippel-Lindau disease, adult polycystic kidney disease, and acquired renal cystic disease from renal failure.[24,31] Histologically, there are three varieties: the classic "clear cell" type characterized by uniformly large, cholesterol-laden cells with small nuclei and rare mitoses; a granular cell type exhibiting a darker staining cytoplasm containing numerous mitochondria and more numerous mitoses; and an uncommon spindle cell (sarcomatoid) variety that has fusiform cells and variation in cell size (Figure 7).

Clinical manifestations. The classic presenting triad of hematuria, flank pain, and palpable abdominal mass is seen in less than 10% of patients and only among those with far-advanced local tumors (Table 3).[3,32,33(p202)] Gross or microscopic hematuria alone, however, is present in approximately

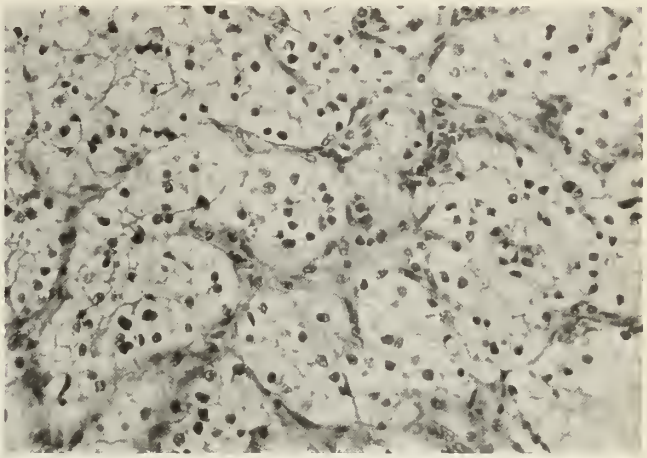

Figure 7.—Classic clear cell pattern of renal cell carcinoma is shown (hematoxylin and eosin; original magnification × 250).

60% of patients with RCC.[3,32,33(p202)] Detection of renal tumors in asymptomatic patients has increased, but 20% to 30% of patients still have local extension or metastatic disease at the time of diagnosis.[34] Because of its protean manifestations and propensity for curious metastatic sites, RCC has been dubbed the "internist's tumor." Indeed, paraneoplastic syndromes are common in patients with RCC (Table 4): pyrexia (the presenting symptom in approximately 15% of cases), hypertension (20% to 40%), erythrocytosis (3% to 6%), hypercalcemia (3% to 6%), anemia (20% to 40%), and hepatic dysfunction (10% to 15%).[35] The paraneoplastic syndromes may raise suspicion of RCC, but they do not suggest metastases. Furthermore, they are not prognostic because removing the primary tumor when there is no demonstrated metastasis usually eliminates the associated syndrome.

Hypercalcemia in patients with nonmetastatic RCC is associated with a tendency toward hypophosphatemia and increased urinary excretion of nephrogenous cyclic adeno-

TABLE 3.—*Presenting Findings in Renal Cell Carcinoma**

Finding	*Occurrence, %*
Hematuria	50-60
Elevated erythrocyte sedimentation rate	50-60
Abdominal mass	24-45
Anemia	21-41
Flank pain	35-40
Hypertension	22-38
Weight loss	28-36
Pyrexia	7-17
Hepatic dysfunction	10-15
Classic triad (hematuria, abdominal mass, flank pain)	7-10
Hypercalcemia	3-6
Erythrocytosis	3-4
Varicocele (left)	2-3

*Adapted from Skinner et al,[3] Chisholm,[32] and Fallon.[33]

TABLE 4.—*Paraneoplastic Syndromes Associated With Renal Carcinoma**

Hypercalcemia	Galactorrhea
Nonmetastatic hepatopathy	Cushing's syndrome
Hypertension	Gynecomastia
Erythrocytosis	Serum glucose abnormalities
Pyrexia	Amyloidosis

*Adapted from Sufrin et al.[35]

sine monophosphate. It was originally thought to be secondary to ectopic production of parathyroid hormone (PTH). The hypercalcemia has now clearly been shown to be secondary to secretion of a novel peptide hormone termed PTH-related protein, which has considerable homology to PTH in structure and in biologic activity.[36] The serum calcium level returns promptly to normal levels after successful removal of the RCC.

Nonmetastatic hepatopathy, also called the nephrogenic hepatic dysfunction syndrome or Stauffer's syndrome, describes a disorder of unknown pathogenesis and nonspecific hepatic histology in which hepatic function is deranged in patients with renal cell carcinoma. Most common are elevations of serum alkaline phosphatase and globulin levels with prolongation of both the prothrombin time and the excretion of sulfobromophthalein sodium. The serum albumin level is frequently reduced, and more rarely the aspartate aminotransferase level is increased. Hepatosplenomegaly may accompany these functional derangements, all of which return to within normal limits after surgical removal of the tumor. Hypertension in patients with an RCC may be "essential" and unrelated to the tumor or may be secondary to an increased production of renin. Anemia is frequently found and usually represents the anemia of chronic illness with decreased red blood cell survival and poor marrow responsiveness rather than iron loss from hematuria. More striking, however, is the erythrocytosis that occurs in 3% to 6% of patients, which is caused by the secretion of erythropoietin by the tumor. Renal cell carcinoma is one of the malignant tumors, like the lymphomas, that is most frequently associated with fever. The fever is often intermittent and is thought to result from the release of endogenous pyrogens from the tumor itself.

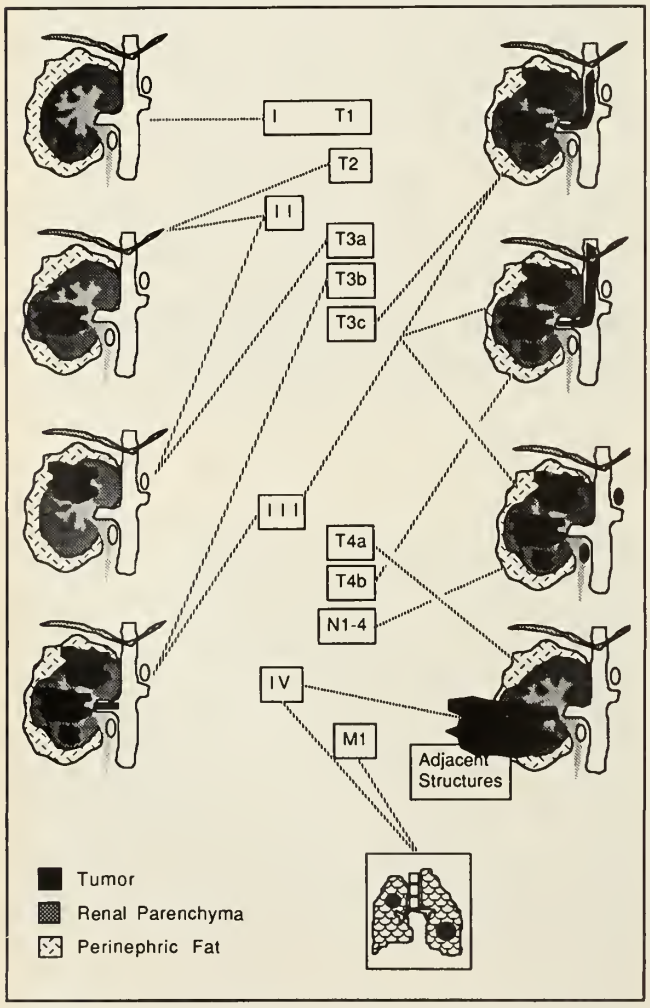

Figure 8.—Robson **(left column)** and TNM **(right column)** staging systems for renal cell carcinoma are depicted.

Rarely, RCC manifests first with the acute onset of a varicocele, especially in the left scrotum. The left gonadal vein normally drains into the left renal vein, where it may be obstructed by thrombosis or by direct extension of the tumor into the renal vein.

Diagnosis. There is no specific diagnostic laboratory test for RCC. The diagnosis must be considered in patients with unexplained constitutional symptoms or hematuria. The diagnostic evaluation relies on the algorithm described previously for the investigation of a renal mass or hematuria.

Therapy. Therapy is dictated by the stage of the disease. The TNM and Robson staging classifications are summarized in Figure 8.[37] The local extent of the disease is most commonly determined by CT scan, which must address direct local extension to other organs, lymphatic spread, and tumor extension into the renal vein or inferior vena cava. The functional status of the contralateral kidney is important in determining the therapeutic options. Hematologic metastatic tumor spread commonly involves the lungs, bones, or both. Routine staging should also include a chest radiograph, bone scan, and serum alkaline phosphatase measurement.

The treatment of patients with stage T1, N0, M0 through T4b, N0, M0 consists of radical nephrectomy, which by definition includes the removal of Gerota's fascia and its contents (kidney and adrenal gland) as well as the regional draining of the lymph nodes. The value of an extended lymphadenectomy in treating patients with occult nodal disease is currently an issue of debate.[38] A unique surgical dilemma that merits comment is the patient who presents with synchronous bilateral RCC or RCC in a solitary kidney. Recent experience indicates that parenchyma-sparing procedures are not only technically feasible but also provide excellent control of the neoplastic lesion.[39,40]

Prognosis. The pathologic tumor stage remains the most important predictor of survival rate.[41] The stage demonstrates a significant correlation with both nodal and distant metastatic involvement. These two indicators in turn are highly predictive.[42] Patients without nodal or metastatic involvement at the time of tumor removal have a five-year survival rate ranging from 50% to 70%. This is in sharp contrast to patients with metastatic tumor, whose five-year survival ranges from 0% to 5%. Nodal involvement alone carries an intermediate prognosis with five- and ten-year survival rates of 52% and 26%, respectively.[43] The prognostic significance of a tumor thrombus of the renal vein or vena cava is less clear. Although it appears that a subset of patients with venous extension alone may be cured by an appropriate surgical procedure, this feature is often associated with factors that adversely influence prognosis.[42,43] Patients whose tumors have a spindle cell pattern histologically have a poorer prognosis than those with other histologic types.[44]

Flow cytometric analysis of DNA ploidy has been used in an effort to identify other prognostic variables. Preliminary results from these studies suggest that renal cell tumor DNA ploidy is not an independent predictor of outcome.[45,46]

Approximately 25% of patients present with dissemi-

nated disease at the time of diagnosis, with an additional number manifesting metastasis after a nephrectomy.[3] With rare exceptions, the management of these patients is palliative or experimental. One exception is those patients who have a solitary surgically resectable metastasis temporally remote from their nephrectomy. Survival for five years has been reported in as many as 35% of these patients.[47]

Most patients with metastatic disease die despite treatment. Multiple chemotherapeutic and immunotherapeutic agents, alone or in combination, have been used in attempts to treat this neoplasm. Of 39 new agents evaluated in 2,120 patients from 1983 through 1989, a total response rate (either complete or partial) of 8.77% was observed.[48] This disappointing response rate may result in part from high levels of multiple drug resistance (MDR1) gene expression by these tumors.[49]

The success of biologic response modifiers, alone or in combination, is similar.[50] Initially there was enthusiasm for the combination of interleukin 2 and lymphocyte-activated killer cells based on the reported experiences at the National Cancer Institute. Subsequent multicenter trials, however, have failed to substantiate the initially reported 30% activity of this regimen.[51,52] Recombinant human interferon alfa, which has had an average total response rate of 16%, may represent a reasonable treatment option, particularly in view of its mild toxicity and ease of administration.[50]

Nephrectomy is of little use in treating a patient with metastatic disease.[53] Early reports, which suggested that nephrectomy might lead to a spontaneous regression of metastases, failed to establish cause or to consider surgical mortality. Most contemporary studies have failed to show any benefit from palliative nephrectomy in an otherwise asymptomatic patient. Patients with intractable pain, hematuria, retroperitoneal blood loss resulting from the primary lesion, or severe symptoms associated with a paraneoplastic syndrome may be considered for palliative nephrectomy. Angiographic renal artery embolization, and a variety of analgesic or anesthetic techniques, are usually preferable, however, given the mortality and morbidity associated with nephrectomy in these patients. Palliative nephrectomy is currently indicated only in patients who fail to respond to these measures or as adjunctive therapy as part of a prospective controlled clinical trial. Radiation therapy has not proved beneficial in a primary or adjuvant curative way. It is, however, useful in palliating symptoms attributable to locally recurrent or metastatic disease.[54]

Although the disease is varied in its individual behavior, the overall prognosis for patients with metastatic renal carcinoma is poor. Median survival rates for the "best risk" and "worst risk" groups are 12.8 months and 2.1 months, respectively.[55]

Nephroblastoma

Nephroblastoma (Wilms' tumor) is the most common malignant neoplasm of the urinary tract in children, accounting for 8% of all childhood tumors.[56] It is diagnosed in a third of the cases when the child is younger than 2 years and in two thirds of the cases when the child is younger than 4 years.

Clinical manifestations and diagnosis. The tumor is palpable in as many as 80% of cases and is often discovered by a parent. Pain is initially present in 50% of patients, hematuria (usually microscopic) in 10% to 20%, and hypertension in approximately 60%.[57,58] The diagnosis is usually established first by intravenous pyelography, which commonly shows caliceal distortion. Calcification within the mass occurs in 10% to 15% of patients. Abdominal ultrasonography or CT scans are useful to determine tumor extension and the possibility of involvement of both kidneys. This occurs in approximately 10% of patients. Arteriography is rarely used.

If the diagnosis remains uncertain after these studies are performed, the measurement of urine vanillylmandelic acid levels should help rule out neuroblastoma. Evaluation for the presence of metastases should be directed to the lungs, liver, and opposite kidney. A roentgenogram and CT scan of the chest and a CT scan of the abdomen are sufficient. Nephroblastoma, as with RCC, often produces a tumor thrombus in the inferior vena cava, which may have to be delineated by venacavography. Abdominal ultrasonography is also a reasonable alternative to establish this possibility.

Treatment. The development of a successful treatment for nephroblastoma is rightfully heralded as one of the most important advances in cancer therapy in the past few years. In the absence of distant dissemination or an unfavorable histologic finding, the prognosis has improved from a 25% survival rate in the 1960s to more than 90% currently.[59]

The initial treatment of nephroblastoma is complete surgical removal of the primary tumor and kidney even when there are metastases. A transabdominal approach provides the safest access and the necessary exposure of the liver, para-aortic nodes, and contralateral kidney for complete staging. Occasionally, radiotherapy or chemotherapy may be required preoperatively to decrease the bulk of massive tumors. Combined therapy is indicated postoperatively in all patients but is dependent on accurate staging, completeness of surgical extirpation, and tumor type. A tumor confined to the kidney in a child younger than 2 years requires only the postoperative administration of dactinomycin and vincristine sulfate, whereas in all others the best results are obtained with radiation therapy to the tumor bed plus the administration of dactinomycin and vincristine. Doxorubicin is also an active agent in treating this disease. Additional areas of current investigation are radiation therapy and the addition of doxorubicin to a regimen of vincristine and dactinomycin for patients with extensive local disease and favorable histologic appearance and radiation therapy with triple drug versus quadruple drug (addition of cyclophosphamide) for patients with unfavorable histologic type (anaplasia or sarcomatous elements). Wilms' tumor may occasionally be seen in adults; similarly, RCC occurs rarely in children.[60]

Tumors of the Renal Pelvis, Ureter, and Bladder

The urinary tract is lined with transitional epithelium from the level of the calices to the proximal urethra. Neoplastic processes arising from this lining account for more than 90% of all tumors involving the upper and lower urinary tract collecting systems.[61] This epithelium undergoes neoplastic transformation as a result of contact with carcinogens in the urine. Environmental carcinogens excreted in the urine come in intimate contact with the epithelial surface for prolonged periods of time, resulting in the classic induction and promotion phases associated with chemical carcinogenesis.[62] The diffuse nature of urothelial exposure to carcinogens often results in multifocal areas of dysplastic and neoplastic change.[63,64]

Uroepithelial neoplasms have a 4:1 male-to-female preponderance and typically occur in the sixth and seventh dec-

ade of life. There is, however, a broad range from the pediatric to the geriatric population. A number of environmental risk factors have been identified, including cigarette smoking, exposure to certain industrial chemicals, particularly aromatic amines, and long-term abuse of phenacetin-containing analgesics.[65-67]

The remaining 10% of tumors involving the urinary tract collecting system are composed of a diverse histologic group including squamous cell carcinoma, adenocarcinoma, and sarcoma. Squamous cell carcinoma probably arises from the transitional epithelium via the process of squamous metaplasia associated with chronic inflammatory changes. Indwelling foreign bodies (catheters) and parasitic infections involving the bladder wall (schistosomiasis) are associated with an increased risk of squamous metaplasia and neoplasia.[68,69]

Adenocarcinomas involving the urinary tract are typically limited to the urinary bladder. Although transitional epithelium may undergo adenomatoid metaplasia, most adenocarcinomas of the bladder are thought to arise from embryologic hindgut remnants such as a persistent urachus in the dome of the bladder.

Tumors of the Upper Urinary Tract

Transitional cell neoplasms involving the upper urinary tract account for less than 10% of urothelial tumors.[70] These lesions may occur anywhere along the course of the upper tract collecting system but most frequently in the distal ureter.[71] Hematuria remains the most common presenting symptom, occurring in as many as 80% of patients.[72] Although ureteral obstruction with superimposed hydroureteronephrosis will develop in 40% to 50% of patients, renal colic is rare because of the insidious onset of the obstruction.

Figure 9.—A retrograde pyelogram shows the classic goblet sign caused by the intraluminal filling defect resulting from a ureteral transitional cell neoplasm.

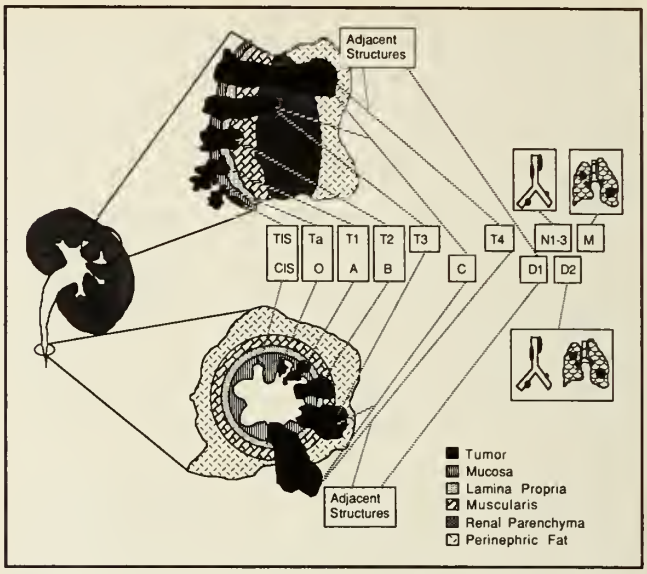

Figure 10.—The TNM (upper) and Jewett (lower) staging classifications for transitional cell neoplasms of the upper urinary tract are depicted.

Excretory urography followed by cystoscopy constitutes the initial diagnostic evaluation. In cases in which renal nonfunction secondary to long-standing obstruction precludes unilateral excretion of contrast medium, or when excretory urography is nondiagnostic, retrograde pyelography is the study of choice. Further evaluation may include cytologic studies of the upper urinary tract and direct visualization and biopsy with rigid or flexible ureteropyeloscopy. Care should be taken to exclude other radiolucent ureteral filling defects that include sloughed papillae, radiolucent stones, and fungus balls. Figure 9 shows the classic goblet sign, which is characteristic of ureteral transitional neoplasms.

Treatment is determined by the location, stage, and grade of the tumor and the status of the contralateral kidney. Chest radiograph, abdominal CT scan, and bone scan are necessary to determine the local and systemic extent of disease. Because of the difficulty in excluding local invasion, most patients with these lesions are treated with extirpative surgery. As a result of the unique propensity of these tumors for downstream metachronous recurrence, tumors involving the renal pelvis or calices, or both, have traditionally been treated with nephroureterectomy. Depending on the stage and grade, distal ureteral tumors may be amenable to local excision with subsequent ureteral implantation.[73] Highly selected groups of patients with unifocal, low-grade, low-stage neoplasms, or a contraindication to nephrectomy, have been managed successfully with endoscopic tumor ablation.[74]

The prognosis for these patients is stage- and grade-dependent. Figure 10 outlines the TNM and Jewett staging systems used for ureteral and upper tract transitional cell neoplasms. Fortunately, most are of low stage and grade and, therefore, have an excellent prognosis. Muscle invasion and direct local extension are poor prognostic signs.

The high rate of downstream metachronous tumor recurrence in these patients necessitates careful follow-up. Although a lesion develops in the contralateral upper urinary tract in less than 5% of patients, 50% to 60% of patients eventually have a bladder neoplasm.[75,76] For this reason, it is recommended that cystoscopy be carried out every three

months until the patient remains tumor-free for a period of a year. Semiannual or annual surveillance is then warranted.

The prognosis for patients presenting with or subsequently developing metastatic disease is poor. Recent improvements in the treatment of transitional cell carcinoma of the bladder using multidrug chemotherapy are promising, however, and support the use of these regimens in the treatment of disseminated transitional cell carcinoma of the upper urinary tract.[77]

Tumors of the Urinary Bladder

In 1992, approximately 50,000 new patients will present with tumors of the urinary bladder, 90% of which will have a transitional histologic appearance.[78] Hematuria is the most common presenting sign. When present, gross hematuria is typically total and painless. Irritative voiding symptoms, including frequency and dysuria, are additional common findings. Bladder irritability, with detrusor instability, represents a "final common path" response of the bladder to a spectrum of pathologic processes. Although this is commonly associated with bladder outflow obstruction due to prostatism, the clinician must be careful not to ascribe isolated symptoms of bladder irritability prematurely to prostatism in men in the age group at risk for both prostatism and urothelial malignancy.

The diagnostic workup is identical to that described for lesions of the upper urinary tract. Careful cystoscopy with urinary cytology is sufficient to preclude the presence of disease of the lower urinary tract. When identified, bladder abnormalities should be treated with transurethral excisional biopsy and bimanual bladder examination under anesthesia. Selected mucosal biopsies of adjacent areas of urethral abnormality may be necessary to define the presence of associated carcinoma in situ. For high-grade appearing lesions, and those involving the bladder neck, transurethral prostate biopsies are recommended to exclude prostatic duct or stromal involvement. The stage and grade of the tumor defined by excisional biopsy dictate further evaluation and therapy. Tumors are broadly divided into superficial and invasive categories. Figure 11 shows the TNM and Jewett classifications for neoplasms of the bladder. Tumors of T stage T1 or less are defined as superficial, with stage T2 or greater defined as invasive.

Superficial Bladder Carcinoma

Of patients with carcinoma of the bladder, 70% have superficial lesions at presentation.[79] The major disease-related issues for this group of patients can be divided into the risks of tumor recurrence and tumor progression.

The biologic behavior of superficial bladder carcinoma is characterized by polychronotropism, that is, multiple occurrences in space and time. One-year and overall recurrence rates of 56% and 70%, respectively, have been reported.[80,81] The cause of this exceptionally high rate of recurrence is unclear. Urothelial field change disease resulting from diffuse urothelial contact carcinogenesis clearly plays some role.[82] When metachronous recurrence rates of other organs at risk for diffuse contact carcinogenesis are compared, such as the nasopharynx, lungs, stomach, and colon, the bladder is unique in both the frequency and pattern of recurrence.[83-87] This finding is particularly striking considering the low grade and otherwise low malignant potential of most superficial bladder neoplasms.

Tumor implantation is a unique mechanism that may account for the idiosyncratic behavior of superficial bladder carcinoma.[88-92] Transurethral bladder tumor removal is novel in that it releases large numbers of viable tumor cells into a fluid medium in direct contact with areas of bladder

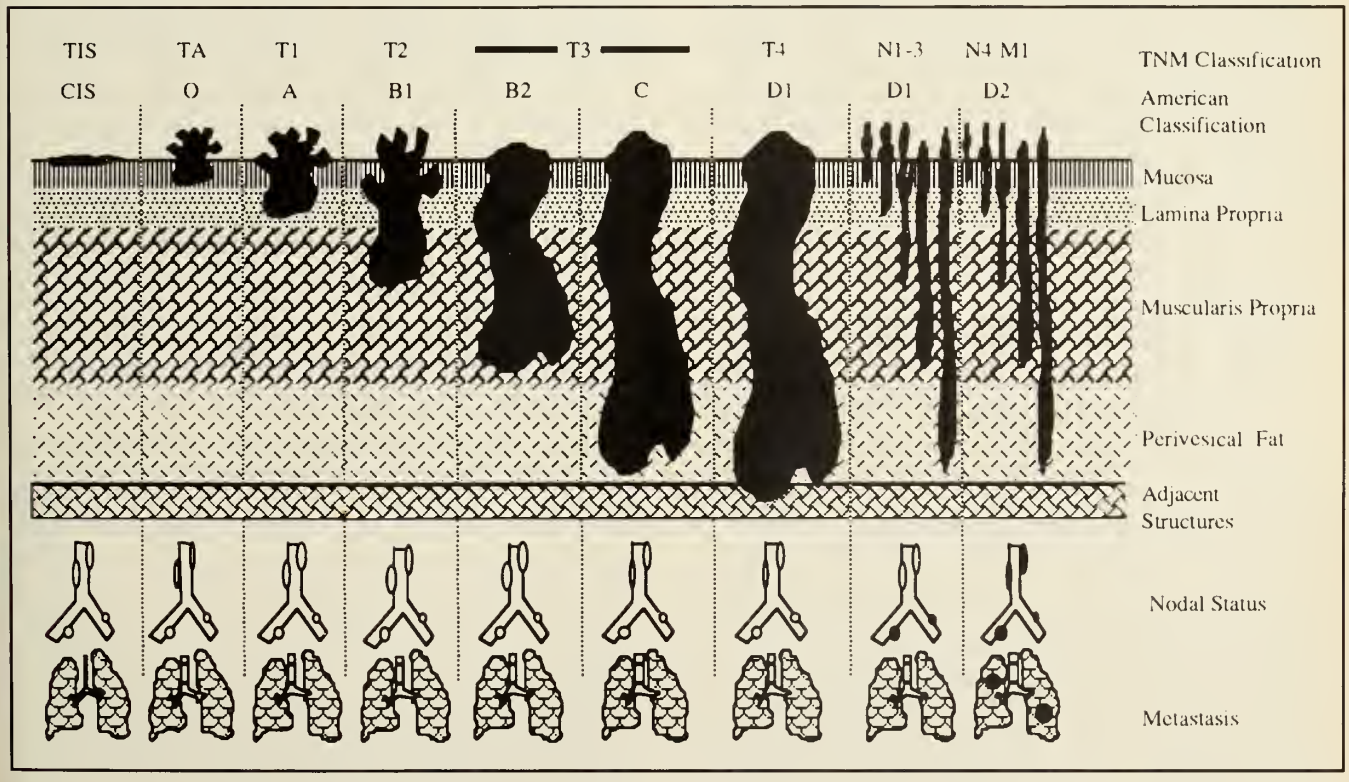

Figure 11.—The TNM **(upper)** and Jewett **(lower)** staging classifications for neoplasms of the bladder are shown.

injury. In vivo studies have shown that areas of urothelial injury represent preferential sites for tumor cell adherence and growth.[93,94] A number of iatrogenic and tumor-associated variables including concentration of tumor cells, surface area of urothelial injury, duration of urothelial exposure, and intravesical pressure at the time of exposure demonstrate a positive correlation with the size of the adherent inoculum.[95] The size of the adherent inoculum in turn determines the risk of tumor growth.

An additional iatrogenically mediated factor that may influence implantation-associated recurrence is the local milieu at the site of tumor cell adherence. Traumatic urothelial injury initiates the process of epithelial repair involving cell division, migration, and neovascularization. The same factors that regulate normal reparative processes may influence the growth of tumor cells adherent to the injury site.

To date, only tumor size and the number of tumors at presentation have correlated with risk of recurrence.[96,97] Bladder tumor recurrence is a cause of significant patient morbidity, but it is rarely life threatening. A subset of patients at high risk for recurrence based on their presentation may be treated in an effort to prevent recurrence, but usually therapy is withheld until the time of first tumor recurrence. Therapy to prevent recurrence is founded on the intravesical administration of chemotherapeutic or immunotherapeutic agents. Thiotepa, adriamycin, mitomycin, and bacillus Calmette-Guérin (BCG) vaccine have been administered in an effort to decrease recurrence rates.[98] In selecting an agent for intravesical therapy, the clinician must weigh not only the risk of recurrence but also the potential for disease progression as well as the toxicity associated with the chosen therapeutic agent. For patients with low-stage, low-grade lesions at low risk of progression, thiotepa represents a reasonable initial choice.

Tumor progression. The risk of tumor progression, defined as recurrence at a higher tumor stage, depends on initial tumor stage and grade. Although less than 2% of patients with grade 1, T0 lesions ultimately have disease progression, 69% to 83% of patients with grade 3 lamina propria invasion and associated carcinoma in situ have recurrence as muscle invasive disease.[99] Because disease progression is potentially fatal, careful attention must be paid to individual risks of patients for this phenomenon. Patients at high risk must be followed closely with cystoscopy, biopsy, and urinary cytology and the most effective agent chosen for first-line therapy. All patients at high risk for disease progression should be treated at the time of presentation. Intravesical BCG administered in six weekly courses of 120 mg is the therapeutic agent of choice. Patients failing a six-week induction course of BCG may benefit from an additional six-week course.[100] Maintenance BCG therapy appears to be of little benefit.[101] Patients in whom a second induction course fails are at high risk for tumor progression and disease-related death and should be considered for exenterative surgery.

Although it is categorized with the superficial bladder carcinomas, carcinoma in situ represents an aggressive form of urothelial neoplasia. Carcinoma in situ, either alone or in conjunction with papillary neoplasia, frequently progresses to muscle invasion and may represent the precursor lesion to invasive disease. Patients with isolated or mixed lesions containing carcinoma in situ should be treated aggressively with intravesical BCG at the time of presentation. Persistently positive cytologic studies of the bladder after therapy in the presence of negative results of mucosal biopsy of the bladder may indicate persistence of disease in the upper urinary tract or prostatic fossa.[102,103]

All decisions regarding the management of patients with superficial bladder carcinoma must be based on adequate biopsies of the bladder. The absence of muscle in the biopsy specimen suggests inadequacy of the specimen and the need for additional tissue.

Muscle Invasive Bladder Carcinoma

Tumor stages greater than or equal to T2 constitute invasive disease. The overall 50% disease-related mortality for patients with this stage of disease is indicative of its aggressive nature.[104] Treatment options are determined by the local extent of disease and the presence of systemic spread. The staging evaluation should include a chest radiograph, abdominal and pelvic CT scans, and a bone scan. If cystectomy is a consideration, the decision regarding concomitant urethrectomy and urinary diversion options depends on the degree to which the disease has extended into the prostatic fossa and proximal urethra. For this reason staging should include biopsies of these sites.

Treatment options for patients with organ-confined disease include radical radiotherapy or cystectomy. Data suggest that radical cystectomy confers the greatest likelihood of cure.[105] Advances in modern urologic oncology in the 1980s have greatly reduced the morbidity and mortality associated with radical cystectomy. Selected patients may be candidates for potency-sparing dissections.[106] New methods of continent urinary diversion afford improved body image and quality of life for both men and women.[107,108] Studies have failed to show additional benefit from preoperative adjuvant radiotherapy.[109]

Patients who refuse or are not medically fit to undergo radical cystectomy may benefit from definitive external beam radiation. Radiation therapy alone or in combination with a chemotherapeutic radiation sensitizer, such as fluorouracil or cisplatin, has been administered with curative intent.[110,111]

The identification of platinum-based regimens with activity against transitional cell carcinoma in the mid-1980s has had a notable effect on the management of this disease.[112,113] The role of these regimens in the management of patients with regionally confined disease remains undefined. The appropriate candidates for therapy, the optimal treatment regimen, the timing of drug administration (adjuvant versus neoadjuvant), and the number of treatment cycles have yet to be determined. Until these issues are resolved by ongoing multicenter clinical trials, chemotherapeutic treatment of patients with organ-confined transitional cell carcinoma must be considered experimental.

In contrast to patients with organ-confined disease, multidrug chemotherapy has a clear role in treating patients with disseminated transitional cell carcinoma. The two commonly used regimens with proven activity are MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) and CMV (cisplatin, methotrexate, and vinblastine). Total response rates ranging from 40% to 71% have been reported for these regimens.[113,114] Although most (>95%) patients eventually die of their disease, survival increases an average of four months compared with treatment with cisplatin alone.[115]

When treatment is administered in the neoadjuvant setting (before a planned cystectomy), a significant percentage (30%) of patients have been found to have no histologically

identifiable disease (stage P0) at the time of radical cystectomy. Unfortunately, attempts to define this patient population preoperatively have met with a significant incidence of understaging. In addition, carcinoma in situ, which is commonly associated with muscle invasive disease, is poorly responsive to currently used regimens and may represent a sanctuary lesion that predisposes to disease recurrence.[116] For these reasons, further studies will be necessary to determine the ability of neoadjuvant therapy to serve as a bladder-sparing treatment alternative.

Nontransitional Cell Bladder Neoplasms

Nontransitional cell bladder neoplasms account for less than 10% of all bladder tumors, with the most common histologic types being squamous cell, adenocarcinoma, and sarcoma. Squamous cell carcinoma and adenocarcinoma are commonly seen in adults and are usually invasive at presentation. These are aggressive radioresistant neoplasms that do not respond to drug regimens that proved efficacious against transitional cell lesions. Surgical extirpation of organ-confined disease at the time of presentation affords the greatest chance of cure.

Rhabdomyosarcomas of the prostate and bladder are unusual lesions observed in children. Therapy consists of surgical extirpation in combination with neoadjuvant and adjuvant combination chemotherapy. This multidisciplinary approach has afforded some improvement in the extremely poor prognosis for these patients.[117]

Summary

Neoplastic diseases of the kidneys and urinary collecting system are relatively common, but when detected early, they have an excellent prognosis. Because gross or microscopic hematuria may be an early harbinger of genitourinary pathology, the primary care physician and internist play an integral role in diagnosing these diseases. A high index of suspicion together with a thorough history, physical examination, and appropriate diagnostic studies will enable the correct diagnosis and improved patient management in most cases.

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Epitomes

Important Advances in Clinical Medicine

Preventive Medicine and Public Health

The Scientific Board of the California Medical Association presents the following inventory of items of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in preventive medicine and public health that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Using Health Risk Appraisal in Clinical Practice

A HEALTH RISK APPRAISAL (HRA) is an educational and health promotion tool used to assess health-related behaviors and their effect on mortality risk. Risk factors measured are those that can be modified—smoking, diet, and seat-belt use—and those that cannot—family history, race, and sex. Data are used to estimate a person's risk group (risk cohort), which is based on epidemiologic and actuarial data, and also a person's achievable risk, based on the estimated decrease in risk if positive behavior changes were made. In addition, the relative weight of each of the variables is reported.

Factors to be considered in choosing a health risk appraisal program include the method of administration, the scientific documentation supporting the program, the cost of obtaining and entering the data, and the staff available. Self-administered programs, done directly on the computer or through the mail, use HRAs that are calculated on self-reporting alone. By contrast, there are programs using extensive clinical evaluations, which may include electrocardiograms and physical examinations and require skilled staff to administer. Intermediate types of programs require measuring only height, weight, blood pressure, cholesterol levels, and self-reporting. These intermediate programs are well suited to outpatients. Examples include the Healthier People HRA program developed by the Carter Center at Emory University School of Medicine, Atlanta, Georgia, and the Centers for Disease Control HRA program.

Health risk assessment is useful in determining the health status of people in the workplace, clinic, schools, health fairs, and voluntary and government agencies. The ability of a program to change behavior is influenced by the way the results are given. Program results may be self-interpreted or given by a physician or counselor. One benefit of providing personal counseling is to emphasize the limitations of health risk assessment; clients should understand that HRA does not replace a physical examination and cannot be used in persons with symptoms. Counseling provides an opportunity to explain the results and to refer the client to health promotion programs or health professionals. All of these approaches lead to improved compliance with recommended behavior changes. In multicultural populations, individual counseling provides an opportunity for linguistic and cultural interpretation.

In the outpatient clinical setting, health risk appraisals can motivate patients to modify behavior detrimental to their health and can identify the need for intervention. Program selection should be based on the needs of the patient population and the scientific basis of the program. Information on different programs can be obtained from the Society for Prospective Medicine, PO Box 55110, Indianapolis, IN 46205-0110.

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Lead Exposure

RECENT WORK has documented an association between blood lead levels in children as low as 10 μg per dl (0.5 μmol per liter) and slight but statistically significant decreases in IQ. A recent meta-analysis confirmed this association. There is a dose-response relationship with a slight but progressive decrease in IQ with increasing lead levels, as well as a "recovery" phenomenon if levels fall below 10 μg per dl (0.5 μmol per liter). This association has been found in the United States and Australia.

There may be no "safe" level of lead in the blood. The level thought to be toxic (25 μg per dl or 1.2 μmol per liter) has recently been lowered by the Centers for Disease Control to 10 μg per dl (0.5 μmol per liter). The environmental fac-

tors that place a person at risk for a single exposure generally remain a long-term threat, particularly in the areas where there are the fewest resources to remove them. For these reasons, children living below the poverty level, the uneducated, and certain races may be more likely to have exposure to a substance that will retard their development and are less likely to have the means or the political clout to correct the problem. Conversely, all groups may be at risk, as young middle-class families renovate their "new" old homes peeling with lead-based paint, use lead-containing folk remedies, and drink from lead-glazed pottery or leaded crystal.

The ubiquitous presence of lead contamination and the profound economic ramifications of identification and removal threaten to make this issue a political battle as well as a medical one. It can also be an emotional issue—an outcry of anger and protest from "classic car" owners over legislation to ban the manufacture of leaded gasoline is symbolic of the problems of reducing the risk of exposure. While such legislation has eliminated the risk associated with the use of leaded gasoline, owners of older cars believe that the costs of lost engine efficiency, increased valve wear, and fuel requiring expensive additives are not worth the theoretic benefit to the rest of society.

Infant cord blood lead levels (implying prenatal exposure) are well correlated with deficits in visual-spatial and visual-motor integration skills at the age of 24 months. A level of "recovery" occurs with many children after 24 months that is not directly related to the initial level but, rather, with factors such as social class, maternal IQ, and with subsequent measured levels of lead. This suggests that children raised in adverse environments will show a deficit at blood levels lower than those seen to affect children of a more advantaged social class.

What are the sources of lead that make this such a pervasive problem? Exposure has been shown to occur through leaded gasoline fumes, proximity to smelter plants, ingestion of lead-containing paints, drinking water that has passed through pipes welded with lead-containing compounds, and hobbies that involve the melting of lead to make fishing weights, model figures, and stained glass. A recent study reported that lead in labels printed on soft plastic bread wrappers could leach into food if the bags were inverted before reuse.

The issue of treatment is unclear. The easily recognized "toxic" levels of lead in the blood—more than 60 μg per dl or 2.9 μmol per liter—may be cleared through a variety of means. Penicillamine and ethylenediaminetetraacetic acid (EDTA) are the traditional agents; both are moderately effective yet have risks of their own. An orphan drug, 2,3-dimercaptosuccinic acid, is apparently more effective and better tolerated as a chelating agent. Treating long-term, low-level lead exposure is not nearly as simple in that the only effective management is prevention and modification of the environment. Without satisfactory methods of treatment available, one must question the appropriateness of wholesale screening of persons at low risk.

A recent study demonstrated the feasibility of screening children using blood lead levels in a suburban family practice. It was found that 20% of children had levels between 10 and 25 μg per dl (0.5 to 1.2 μmol per liter), a percentage similar to that reported in a number of other studies. No child in this relatively small sample had levels higher than 25 μg per dl (1.2 μmol per liter), however. Because no treatment is available other than removing the source of exposure when it can be identified, physicians are faced with an overwhelming task. This suggests that continued physician-supported legislative and educational efforts to decrease environmental lead levels are more appropriate.

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Needleman HL, Gatsonis CA: Low-level lead exposure and the IQ of children: A meta-analysis of modern studies. JAMA 1990; 263:673-678

Anticipating the Arrival of Cholera From Latin America

CHOLERA RAISES legitimate fear wherever it has spread because it can cause large, explosive epidemics and lead to death from hypovolemic shock in 12 to 24 hours. The present, seventh pandemic of cholera—caused by toxigenic *Vibrio cholerae* O, biotype El Tor—began in Indonesia in 1961 and spread first to other areas of Asia, the Middle East, and Africa. In late January 1991, it appeared almost simultaneously in five Peruvian coastal cities between Lima and the northern border with Ecuador and, in succession, invaded Ecuador, Colombia, Brazil, Chile, Mexico, Guatemala, Bolivia, El Salvador, and Panama. It has progressed as far north in Mexico as the state of Sonora, just over the border from Arizona.

As of December 1991, more than 360,000 cases had been officially reported from the Americas, at least 158,000 patients had been admitted to hospital, and more than 3,800 had died. In contrast, between 40,000 and 50,000 cases of cholera have been reported annually throughout the world in recent years. Peru alone reported more than 390,000 cases in 1991.

Travelers to South America have already imported cholera to the United States. One had traveled to Peru and four others to Ecuador. In addition to these isolated cases, two small clusters of eight cases in New Jersey and three cases in New York City occurred after travelers brought home cooked crab from Ecuador and shared it with family and friends. There were no secondary cases. Although there have been 41 importations of cholera to the United States from endemic areas of the world between 1961 and 1990, there has not been a single secondary case.

Epidemiologic investigations in different locales in Latin America have identified a number of risk factors such as unchlorinated municipal water supplies, ice made from such water, dipping hands into home water storage vessels intended for drinking, ingesting ceviche (raw marinated seafood), and eating cabbage fertilized with raw sewage.

Cholera has been thought to be spread primarily, if not entirely, by contaminated water. During the past 20 years, however, investigations have shown that foods can be impor-

tant vehicles of transmission. Commonly implicated are shellfish and fish that are eaten raw or undercooked, and cooked foods, such as rice, that are eaten after hours of storage at ambient temperatures.

There is no practical way to keep cholera from being introduced by travelers from Latin America. Travel restrictions at international borders have failed because most persons infected with cholera are asymptomatic; in the first day or two of illness, they may have no vibrios in their stools, and they may evade checkpoints. When, and not if, cholera is imported to California and other parts of the United States from south of the border—just as one or two cases are regularly imported each year to California from other endemic areas of the world—we expect that it will be promptly contained and not followed by large community outbreaks.* The United States has protected water supplies, good water and sewage treatment, and good separation of our sewage systems from our water supply systems. Potential pockets do exist, however, such as migrant labor camps, where infection can be introduced and spread within and among camps. Some local health departments have reviewed the water and sewage systems available in such camps and gained the cooperation of management and of workers in establishing surveillance for clinical cholera.

What will the clues be? Physicians should consider cholera when a person 10 years of age or older has painless, watery, afebrile diarrhea so severe that it can cause severe dehydration or death, especially when the diarrhea is of "rice water" character (sometimes it has a mild, inoffensive fishy odor) and the patient or his or her contacts have recently been in Latin America.

Any suspicion of clinical cholera should be immediately reported to local public health authorities and the stool specimen plated on thiosulfate-citrate-bile salts-sucrose (TCBS) agar, which inhibits the overgrowth of competing microflora. In addition to direct TCBS plating, alkaline peptone water enrichment will enhance recovery of the organism. Cary-Blair is a good transport medium for fecal specimens. Though isolation of *V cholerae* is the preferred way to confirm the diagnosis, laboratory diagnosis can also be made by a notable rise in vibriocidal or antitoxic antibodies between acute- and early convalescent-phase serum specimens in persons not recently immunized.

Treating cholera is simple and straightforward. Most important is prompt fluid and electrolyte replacement to correct volume depletion, acidosis, and electrolyte imbalance. While it was previously thought that intravenous therapy was necessary, we now recognize that only the most severely ill patients and those too obtunded or unable to drink need intravenous therapy. All others can be treated by oral replacement therapy. Details on the preparation and composition of various oral replacement therapies for mild to moderate diarrhea and of intravenous replacement therapy for severe cases are available from state or local health departments.

*Cholera was imported to California on February 14, 1992, when an airline flight that had originated in Buenos Aires, Argentina, and had made an intermediate stop in Lima, Peru, arrived in Los Angeles. Two days later, five passengers were admitted to Los Angeles-area hospitals with severe dehydrating diarrhea; one passenger died. Interviews with 175 of 356 passengers and crew members revealed 56 (32%) with diarrhea in the week following the flight. Of these, 40 (71%) sought medical attention and 7 (13%) were hospitalized. Worldwide, 102 passengers and crew members were eventually found to have laboratory evidence of cholera by positive stool culture or high vibriocidal antibody (minimal attack rate, 102/356 = 29%). No secondary cases were reported among contacts. The epidemiologically implicated food was a seafood salad served on the Lima to Los Angeles leg of the trip (Jason Eberhart-Phillips, MD, Los Angeles County Department of Health Services, oral communication, March 1992). That dish was not provided by the Lima caterer to other planes with US destinations.

While antibiotics are not necessary to treat cholera, tetracycline and other antimicrobial agents do limit the duration and volume of diarrhea and the duration of intestinal carriage of *V cholerae*.

A parenteral cholera vaccine is available, but it decreases the risk of clinical cholera by only 50% and protection lasts only three to six months. The vaccine does not decrease the severity of disease in those in whom cholera develops, and, because it does not prevent asymptomatic infection, it provides little protection against importing the disease. Oral vaccines are under investigation; none have been licensed in the United States.

Travelers to cholera-affected areas should be advised not to rely on the cholera vaccine; to drink only boiled or chemically purified water; avoid ice; eat only those fruits and vegetables that are freshly peeled or cooked; avoid raw or undercooked fish or shellfish; and, perhaps, only swim in chlorinated pools.

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Clove Cigarettes

CLOVE CIGARETTES, also known as "kreteks," are tobacco-containing cigarettes compounded with minced cloves. They have been produced in Indonesia for local consumption and export in Southeast Asia for many years. In the 1970s, they became popular in Australia and in the 1980s became a fad in the United States, especially in California. Adverse publicity over suspected health problems appears to have resulted in greatly reduced consumption after 1984, and they are now uncommon in the tobacco shops, convenience stores, and "head shops" where they used to be sold. No ban or restriction on sales (except to minors) prevents the reintroduction of the product by distributors on a large scale in the future, however.

Clove cigarettes have been used most heavily by younger smokers, reflecting an exotic and "new wave" image. In one survey of adolescents in northern California in 1985, 20% of boys and 26% of girls had experimented with them; their use was associated with the use of other substances as well, mostly tobacco. Clove cigarettes are sweetly aromatic, and some numbing of the mouth occurs. The effect is to remove much of the unpleasantness of cigarette smoking for new smokers. They have been called "trainer" cigarettes.

The active ingredient in clove oil is eugenol, a common topical anesthetic extensively used in dental formulations. Although eugenol appears to be safe when applied topically, inhaling the agent is a new issue.

Adverse health effects are suggested by case reports collected by the Centers for Disease Control and the California Department of Health Services; some are not well documented, but two fatalities have been reported. The best documented case to date suggests aspiration pneumonitis—the eugenol, acting as a topical anesthetic, may impair the swallowing mechanism and compromise the airway. Long-term health effects have not been studied.

Of equal concern has been the potential for conditioning smoking behavior among adolescents. Clove cigarettes are a less noxious smoking habit because of their acceptable taste and an anesthetic effect on mucous membranes that lessens discomfort. The habit had been associated with many social trends important among adolescent peer groups: new wave music, "natural" and herbal products, athletic activity (surfing), exoticism (Indonesian names and brightly colored packages), and parental unawareness (until widespread publicity focused attention on the fad). As such, clove cigarettes may represent a dangerous potential for initiating previously inexperienced smokers to the habit.

The California legislature considered a ban on clove cigarettes in 1989 but declined to take action. Other states have enacted varying measures for control, but because tobacco products are exempted from food, cosmetic, and drug regulatory legislation, there appears to be no legal basis for federal action apart from those provisions that apply to all tobacco products.

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Health and Electromagnetic Fields

Two types of epidemiologic studies have suggested that the health of humans may be affected by exposure to electromagnetic fields (EMF). Occupational studies, using proportional mortality to detect associations between adult cancer and occupational exposure to electromagnetic fields, have produced fairly consistent evidence of a slightly elevated risk of total leukemias and acute myelogenous leukemia among workers with presumed high exposure to EMF. These occupations include telephone line workers, installers, and repairers; telephone and telegraph operators and operators of other communications equipment; photographic equipment manufacturers (including movie projection equipment); and electronic and electrical engineers. These workers have an excess risk of about 20%. Case-control studies have sometimes produced similar risk estimates, sometimes not, and have also produced similar risk estimates for brain tumors, primarily astrocytoma, and a higher risk for breast cancer in men.

Studies using residential wiring measurements have generally indicated an increased risk of childhood leukemia or brain cancer. Exposure measurement has produced a perplexing anomaly, however. In early studies a surrogate measure of EMF was used, consisting of a "wire code" derived from the configuration of the wiring in and around a house and presumably categorizing residences according to the current available to the residence and the EMF field generated. An elevated risk was associated with high-current wiring codes. Later studies, attempting both to replicate and to use more direct measurements of EMF, have nearly always confirmed the association between wiring codes and leukemia or brain cancer at risk levels between twofold and threefold but have failed to find any relationship with more direct measurements of EMF. Although there is a demonstrated relationship between measured EMF and residence wiring codes and between wiring codes and childhood cancer risk, there is as yet no proven relationship between measured EMF and cancer risk.

What do wiring codes actually measure? A number of possibilities have been proposed. Some have suggested that an aspect of EMF other than total hours of exposure may be important, such as the size of the spike in amplitude of electric potential when an alternating current is turned on or the harmonic frequencies to 60 Hz that may be present. Another explanation is that in residences with very high current, the electric ground, which is usually connected to the plumbing, leaches carcinogenic heavy metals from pipes into drinking water by electrolysis.

Electromagnetic field physics and in vitro and in vivo study results have not shed light on this anomaly. Physicists point out that the magnitudes of many of the electric fields under investigation are, at the cellular level, less than those induced by neuromuscular events in the body and that the earth's magnetic field is greater than many of the magnetic fields under consideration. Some biologic effects in vitro and in vivo have been documented, however. Induction of ornithine decarboxylase, taken to indicate a promoter effect, has consistently been shown in various cell lines in response to EMFs induced by alternating current of certain (for example, 16 Hz) but not all frequencies. Raising mice for three generations in a strong electromagnetic field fails to increase the incidence of any malignant neoplasm, but reduced pineal output of melatonin in both rats and humans in response to magnetic fields has been reported. The relevance of this finding to leukemia or brain cancer is not known.

Studies of electromagnetic fields and childhood cancer have focused on exposures resulting either from proximity to high-voltage lines or from residential wiring or appliances. Results of studies of risk using proximity to power lines have generally been negative or, when positive, have suggested dose-response relationships inconsistent with a causal interpretation. The possibility that residential or appliance-related exposures may constitute a risk cannot be discounted, but it has not been confirmed.

Physicians may encounter patient anxiety over exposure to EMFs. Concerned parents may feel safer substituting non-

electric alternatives for analog clocks, hair dryers, electric blankets, or other appliances if they are used frequently near children. It may be useful, however, to consider the relative magnitude of the cancer risk, should it prove to exist. The risk of dying of cancer resulting from EMF exposures at the risk levels reported is less than that from passive exposure to tobacco smoke.

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Alerts, Notices, and Case Reports

Recruitment for the β-Carotene and Retinol Efficacy Trial (CARET) to Prevent Lung Cancer in Smokers and Asbestos-Exposed Workers

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THERE ARE THREE major lung cancer chemoprevention trials under way worldwide. One, the β-Carotene and Retinol Efficacy Trial (CARET), is recruiting subjects primarily in California, Oregon, and Washington. Our purpose in this article is to share information about the design of CARET and the recruitment strategy and to address some questions physicians may raise about their patients who participate in CARET. The investigators welcome referrals to the CARET study centers in Irvine, San Francisco-Vallejo-Santa Clara, Portland, and Seattle (as well as Baltimore and New Haven).

Lung cancer is the number one cancer killer of both men and women in the United States and in an increasing number of other countries. Lung cancers account for 27% of all cancer deaths and 6% of total deaths in the United States, an estimated 143,000 deaths in 1991.[1] Despite aggressive efforts at early diagnosis and multimodality therapy, the five-year survival rate from lung cancers remains miserably low, about 15%.[2] Unlike most common cancers, the causes of lung cancer are well established.[3-5] Thus the National Cancer Institute has placed highest priority on the prevention of lung cancer. Primary prevention requires preventing the initiation of cigarette smoking, assisting cessation of smoking, and protecting people from exposures to asbestos, radon, arsenic, and a few other known pulmonary chemical carcinogens.

(Omenn GS, Goodman G, Grizzle J, et al: Recruitment for the β-Carotene and Retinol Efficacy Trial (CARET) to prevent lung cancer in smokers and in asbestos-exposed workers. West J Med 1992 May; 156:540-544)

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For tens of millions of Americans who have already incurred decades of cigarette smoking exposure and several million Americans who have had considerable occupational exposures to asbestos, especially in West Coast seaports, so-called secondary prevention is essential to overcoming the risk factors already at work. About 75% of men and 50% of women between 55 and 64 years of age are current or former smokers.[6] Without secondary prevention, the increased risk of lung cancer does not decline in former smokers after smoking ceases, even though the relative risks do decline compared with continuing smokers or with persons who have never smoked.[7] Among workers already exposed to asbestos, 4,000 to 6,000 are projected to die of lung cancer per year at least until the year 2000 and up to 8,000 to 10,000 will die of all asbestos-related cancers per year.[8,9]

The rationale for cancer chemoprevention programs is based on interrupting late stages of promotion and progression in the multistage process of carcinogenesis. Such actions are exactly what is needed for high-risk persons to take advantage of the latent period (or "time bomb") of 20 to 40 years between first exposure and peak risk for lung cancer. Among the multiple classes of chemicals with apparent chemopreventive activity, vitamin A (retinol) and β-carotene are leading candidates for efficacy in human beings.[10-12] As described elsewhere, studies in animals, epidemiologic analyses, cell culture experiments, and short-term clinical trials to reverse bronchial metaplasia or buccal mucosa cell micronuclei have laid a strong foundation for direct intervention trials.[13]

Three potentially definitive clinical chemoprevention trials, supported by the US National Cancer Institute, are under way. The Harvard Physicians Study, which was initiated to assess the effect of aspirin on heart disease, was continued to ascertain the effect of β-carotene on overall cancer incidence in 22,000 physicians. The α-Tocopherol–β-Carotene Study was established to test the combination of β-carotene plus vitamin E in the chemoprevention of lung cancer in 29,000 smokers in Finland. Finally, the CARET trial was designed to test the combination of β-carotene and vitamin A in 18,000 smokers and asbestos-exposed workers. The design and recruitment strategy for CARET are described herein.

Subjects in chemoprevention trials are healthy volunteers without cancer, not patients who might tolerate considerable discomfort or risk. Because the risk of lung cancer, even among high-risk asbestos-exposed smokers, is on the order of 1 per 100 per year, it is essential that a chemopreventive regimen be shown to have no major objective or subjective side effects.

Design of CARET

CARET is a two-armed, double-blind, randomized chemoprevention trial to test the hypothesis that the oral administration of β-carotene, 30 mg per day, plus retinol, 25,000 IU per day, will decrease the incidence of lung cancer in heavy smokers and asbestos-exposed workers who have smoked.[14,15]

Choice of Agents

The presumed mechanisms of action of β-carotene and of vitamin A (retinol) are attractive and complementary. β-Car-

ABBREVIATIONS USED IN TEXT

CARET = β-Carotene and Retinol Efficacy Trial
ILO = International Labour Office

otene is an electron-scavenging antioxidant as well as a precursor of retinol. Retinol functions to maintain the differentiated state of epithelial cells, including those in the bronchial epithelium, and inhibits cell growth.[16-18] Retinol and retinoic acid bind to specific proteins in the cell nucleus that then regulate gene expression, probably including tumor suppressor mechanisms. A virtue of these agents is the low expected incidence of untoward effects from the dosages prescribed.

Study Population

The study population consists of two groups of participants, the Vanguard group of continuing participants who were enrolled in the CARET pilot studies during 1985 to 1988 in Seattle, and the Efficacy group of participants whose recruitment in the six cooperating study centers began in 1989. The eligibility criteria for CARET are summarized in Table 1.

TABLE 1.—*Eligibility Criteria for CARET*

Asbestos Workers
- Age 45-69 yr, men
- Current cigarette smoker or ex-smoker (quit ≤ 15 yr ago)
- Extensive occupational exposure
- ≥ 15 yr since first occupational exposure
- Chest x-ray film positive by ILO criteria and/or ≥ 5 yr in high-risk trade completed ≥ 10 yr ago

Smokers
- Age 50-69 yr, men and women
- Cigarette smoking history of ≥ 20 pack yr
- Current smoker or ex-smoker (quit ≤ 6 yr ago)

Exclusions
- History of cancer within 5 yr
- History of liver disease within 12 mo
- SGOT or alkaline phosphatase > 2.5× and 1.5× 95th percentile of normal, respectively
- Vitamin A supplementation > 5,500 IU/d
- β-Carotene supplementation
- Premenopausal status

ILO = International Labour Office
SGOT = serum aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)

The pilot studies identified dosage ranges of retinol and β-carotene that substantially increase serum concentrations of carotene and retinyl palmitate without producing signs of liver toxicity, elevating serum triglycerides substantially, or increasing the prevalence of any relevant symptom or sign (except mild yellowing of the skin among those receiving β-carotene) under a fastidious protocol for assessing symptoms (Table 2).[13] A crucial design feature of CARET is that the 1,029 smokers and 816 asbestos-exposed participants in the pilot studies continue in CARET as the Vanguard population. They accumulated 3,000 person-years of treatment before we began the accrual of the Efficacy population in 1989. The Vanguard participants should reveal any toxicity problems resulting from the cumulative dose of vitamin A, β-carotene, or both, before such problems are encountered in the Efficacy participants.

Smoker participants, both men and women, are recruited primarily from the rolls of various health insurers and health maintenance organizations. The pilot study of smokers had

TABLE 2.—*Monitoring for Potential Side Effects**

Method
Self-reported symptoms and signs: symptom assessment questionnaire administered every 4 mo; symptoms graded on a standardized scale
Physical examination for signs every 12 mo; graded on a standardized scale
Laboratory tests: SGOT, serum alkaline phosphatase
Monitoring of symptoms: anxiety, depression, headaches, bowel movements, nosebleeds, vomiting, weight loss
Monitoring of signs: bone pain, dryness of lips, skin dryness, itching, redness or rash, or yellowing

SGOT = serum aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)

*Any signs or symptoms that persist for 2 wk and reach a predetermined threshold grade are managed by a standard drug challenge approach. The sequence of steps is withdrawal of study vitamins; rechallenge at full dose if symptoms resolve; withdrawal of study vitamins if symptoms recur on rechallenge; rechallenge at half dose if symptoms resolve; and withdrawal of study vitamins if symptoms recur on half dose rechallenge.

four arms (regimens): retinol (25,000 IU per day) plus β-carotene (30 mg per day), each agent alone, and placebos. In the transition to CARET, the participants in the three active treatments were assigned to the active CARET regimen and the placebo group continued to receive placebo. The asbestos-exposed workers were recruited from occupational and pulmonary physicians' practices, federal and state workers' compensation programs, labor unions in the Seattle-Puget Sound area, plaintiffs' attorneys, and the Navy Medical Asbestos Surveillance Program in Bremerton, Washington. The pilot study of the asbestos group began as a two-armed study (placebos versus retinol, 25,000 IU per day, plus β-carotene, 15 mg per day). These participants receive their originally assigned treatments, but the β-carotene dosage was increased to 30 mg per day. Acceptance of the treatment regimen is high, and adherence to dose is more than 90% among active participants.

Extensive assumptions are required to calculate the sample size to achieve a desired statistical power in these kinds of prevention trials.[13,15] The key parameters are the annual incidence of lung cancer in the placebo group after randomization, the greatest potential chemopreventive effect of the intervention, the time lag until full effect, the adherence to the medication schedule, the accrual period, the length of follow-up, the incidence of death from causes other than lung cancer, the loss to follow-up, and the statistical requirements.

For public health purposes, a sizable reduction in the risk of lung cancer is needed to justify a general intervention program. Thus we designed CARET to have 80% power to detect an efficacy corresponding to a maximum chemopreventive effect of 33% reduction in incidence of lung cancer in a fully compliant population of the two high-risk groups combined and, secondarily, 50% reductions in each subgroup alone. Such effects may be feasible, based on the reductions of that magnitude observed in animals, the prompt effects on micronucleus formation and human bronchial biopsy specimens, and the two- to fivefold variation in risk of lung cancer between extreme quintiles or quartiles of β-carotene–vitamin A intake or blood levels.

Imperfect adherence, time lag until full chemopreventive effect, and competing causes of death diminish the observable reductions from 33% to a projected actual reduction of 22%. We down-weight cases of lung cancer that occur within the first two years (linear approach to full preventive effect at two years) to adjust for undetected cancers that may be

present at the time of randomization. We know from studies of serial chest radiographs that most lung cancers grow rapidly once they are detected radiographically; chest roentgenograms at three-month intervals failed to improve clinical outcomes.[19,20] Finally, we know that chemopreventive effects of vitamin A and β-carotene can be observed within several weeks in animal studies, in in vitro studies, and in human intermediate end-point studies. We document marked increases in circulating levels of β-carotene and retinyl palmitate.

The medication rate, a quantification of adherence, is the average fraction of full dose taken. The power of the study will be diluted by participants in the placebo arm taking active agents on their own (especially with all the current publicity about β-carotene and vitamin A and inclusion of these agents in multivitamins) and by participants in the active treatment arm failing to take their capsules—including those who become inactive or are removed from the regimen under our symptom management protocol.

Estimation of loss to competing causes of death is based on actuarial estimates; we allow for higher loss among the asbestos-exposed cohort than among the smokers, mostly because women constitute half of the smokers. We refine sample size and follow-up projections as we accumulate experience with risk factor (age, sex, smoking history), accrual, and adherence data. As long as the attrition is low and the medication rate is high, extension of the follow-up would increase the power.

In summary, using a two-sided test, α .05, with a modified log-rank test statistic down-weighting lung cancer cases occurring during the first two years, we estimate that 4,300 asbestos-exposed workers and 13,600 smokers and former smokers are needed to have a power of .80 (80% probability of detecting a true effect) if follow-up is an average of 6.5 years.[13,15] We project 293 weighted lung cancer cases in the placebo arm and 250 cases in the treatment arm, if the greatest potential chemopreventive efficacy is, indeed, 33%.

Enrollment and Follow-up

Recruitment Goals

The keys to the success of CARET will be to attain the recruitment goals at each study center (Table 3) and then to retain these subjects. The West Coast study centers aim to recruit many additional participants, especially the Irvine center, which was funded in mid-1991.

Contact Schedule

At the first visit, baseline history is obtained. In the asbestos-exposed cohort, a chest roentgenogram for routine and International Labour Office (ILO) interpretations is obtained at the first visit and spirometric measurements at the first and second (randomization) visits. A report is prepared for the participant's personal physician. We use a three-month enrollment period with all participants receiving placebo to assess initial compliance and to obtain laboratory and chest roentgenographic results for determining eligibility before randomization. During the next 12 months we contact the participants every 3 months, alternately by telephone and clinic visit; in subsequent years, clinic visits are annual, with follow-up by telephone at the 4- and 8-month marks of each year. Vanguard participants are seen twice a year, in addition to the two telephone calls, because they serve a sentinel function for detecting possible toxicity related to cumulative dose.

The process of monitoring for possible side effects of the vitamin regimen is outlined in Table 2. The goal is to keep each participant taking as close to the full study dose as possible without experiencing any untoward effects. Participants are followed until a primary or secondary end point is reached or the study is completed, which is projected for 1998.

Endpoints

The primary endpoints are diagnoses of lung cancer. The secondary endpoints are other malignant neoplasms and deaths from lung cancer, other cancers, cardiovascular disease, and all other causes. A well-defined process for evaluating endpoints has been implemented. Each presumed primary endpoint is reviewed by the pathologist for the coordinating center. The pathologist's assessment and other pertinent data are then independently reviewed by two physician members of the CARET endpoints committee. In cases of disagreement, the endpoints committee chair decides or brings the case for discussion in the committee, according to specific criteria. The review classifies the basis for the confirmation of cancer and the contribution of cancer to the death of the participant.

The primary analysis is for the incidence of lung cancer in the two high-risk populations, comparing treatment arm against placebo arm. Secondary analyses look at the effect of explanatory variables such as age, sex, smoking history, threshold grade symptoms and signs, side-effects management reports, compliance estimates, individual medication rates, and endpoint data as well as summaries of occupational asbestos exposure history, chest radiograph ILO interpretation, and periodic spirometry test results for the asbestos-exposed population. Ancillary analyses of interest include potential efficacy against mesothelioma or other cancer sites,

TABLE 3.—*Study Center Recruitment Goals and Progress*

Study Center	Goals: Asbestos	Goals: Smoking	Goals: Total	Randomized as of 3/31/92
Baltimore, Md	800	0	800	805
New Haven, Conn	1,000	0	1,000	821
Portland, Ore	660	4,000	4,660	3,180
San Francisco, Calif	800	0	800	699
Seattle, Wash				
Vanguard	816	1,029	1,845	1,845
Efficacy	201	4,300	4,501	3,204
Irvine, Calif (started late 1991)	0	4,300	4,300	155
Total	4,277	13,629	17,906	10,709

potential efficacy against coronary heart disease and other causes of death, roles of smoking in fibrosis and of fibrosis as an independent risk factor in lung cancer among the asbestos-exposed cohort, variation in β-carotene response among participants on similar dosages, smoking cessation success, and behavioral aspects of participation and compliance.

Common Questions From Physicians

Why do you use two agents? How will you be able to tell which is effective, if there is a favorable result? β-Carotene and vitamin A exert entirely different and quite complementary actions, which may be protective against specific aspects of the late stages of the carcinogenic process. We want to increase our possibility of success; this is more important than differentiating the roles of the two agents, especially since the portfolio of chemoprevention trials supported by the National Cancer Program also includes β-carotene alone (Harvard Physicians Study) and β-carotene plus vitamin E (two antioxidants, Finland trial).

What should I do if a patient of mine, participating in your trial, develops symptoms consistent with vitamin A toxicity? The symptoms of vitamin A toxicity, especially at the moderate dosage used in CARET, are nonspecific and relatively common. We have found no differences to date between the placebo and the treatment arms for any of the symptoms or signs or for liver function assays. Therefore, it is unlikely that headaches, change in bowel function, anxiety, depression, and the other monitored symptoms that do occur are due to the regimen administered in CARET. Sometimes specific causes can be ascertained, ranging from personal losses leading to depression to intercurrent infections causing local or systemic symptoms. We have a careful symptom management protocol, however (Table 2).

Does the treatment increase serum triglyceride or cholesterol levels? Should patients with moderate or high levels be excluded from CARET? We found no progressive increase in serum triglyceride levels and no exaggerated response in participants with initial elevated values. Serum cholesterol levels decrease slightly. Thus, we do not exclude subjects from CARET or stop the dosage based on the triglyceride or cholesterol values.

If the treatment is so benign, why not have patients just take β-carotene or even both agents on a prophylactic basis? The US Food and Drug Administration and National Cancer Institute have recently stated that use of these agents to prevent cancer is still experimental and that studies like CARET are essential to ascertain efficacy and to demonstrate safety.

Is β-carotene desirable as an antioxidant to prevent progression of atherosclerosis? Investigators in the Harvard Physicians Study reported that a small subgroup of their subjects receiving β-carotene seemed to have a lower incidence of cardiovascular endpoints.[21] This is stimulating plans for new studies.[22] These investigators and others have warned that any conclusions are grossly premature. The CARET study will provide a good opportunity to test this hypothesis.

Might β-carotene and vitamin A help against other cancers besides lung cancer? It is possible. We are specifically evaluating mesotheliomas in the asbestos-exposed cohort and are checking against a possible increase in prostate cancer, based on some unconfirmed epidemiologic associations. Other cancers do not occur frequently enough to have useful statistical power even in 18,000 older adults, but all cancer cases and all deaths are being analyzed.

How can I assist? We are eager to have referrals for CARET of potentially eligible and interested men and women. Furthermore, we are dependent on the participants' physicians to understand enough about CARET to be supportive of the project and to reinforce our efforts to keep our participants on the annual schedule for visits and on the dosage regimens. We welcome inquiries and referrals to the study centers (Table 4).

Conclusion

Several lines of research suggest that retinol, β-carotene, or both, may be effective and safe chemopreventive agents for lung cancer. Currently, two large studies are testing this

TABLE 4.—*β-Carotene and Retinol Efficacy Trials (CARET) Study Centers and Management*

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hypothesis and one is examining its preventive effect for all cancers.

The CARET study reported here evolved from successful pilot programs. It is unique in that its participant group consists of both smokers and asbestos-exposed workers and also that its regimen is a combination of β-carotene and vitamin A. It includes women as well as men.

Experience with prevention trials has shown some important differences in design and conduct from treatment studies. These differences include the problems of recruiting large numbers of participants from populations not experiencing current illness and maintaining them on the study treatment for long periods of time while monitoring to protect them against side effects. In addition, there are management problems because of the scale of the operation. Participants in prevention trials are partners in research; they are not patients.

We expect CARET, combined with the results of the other two major trials, to determine by the end of the decade whether or not vitamin A and β-carotene can be recommended to occupationally defined high-risk groups and to the public as chemopreventive agents against lung cancer.

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Sarcoidosis Presenting With an Unusual Erythematous Rash and Persistent Hypercalcemia

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SARCOIDOSIS HAS been defined as a multisystem granulomatous disorder of unknown etiology that most commonly affects young adults and most frequently manifests initially with bilateral hilar lymphadenopathy, pulmonary infiltration, and skin or eye lesions.[1]

I describe the case of a patient who had an unusual erythematous annular rash and persistent hypercalcemia as the first signs of the disease. This case illustrates the wide variety of clinical manifestations of this fascinating disease.

Report of a Case

The patient was a previously healthy 61-year-old man who five months before admission had acute iritis, which was treated with topical corticosteroids. Subsequently, intermittent low-grade fevers, drenching night sweats, fatigue, loss of appetite, and an 11-kg (25-lb) weight loss developed.

Three months before admission, laboratory evaluation by another physician yielded the following results: serum calcium 3.12 mmol per liter (12.5 mg per dl), albumin 32 grams per liter (3.2 grams per dl), urea nitrogen 12.85 mmol per liter (36 mg per dl), creatinine 159 μmol per liter (1.8 mg per dl), and a nonreactive rapid plasma reagin test. The erythrocyte sedimentation rate and results of thyroid function tests were within normal limits. The chest roentgenogram showed a small calcified granuloma in the left mid-lung and minimal change from a film obtained 12 years before. Results of renal function studies and serum calcium measurements were within normal limits three years earlier.

Six weeks before admission, a nonpruritic erythematous rash developed on the patient's back and spread to the chest and extremities. Ultrasound studies revealed hepatosplenomegaly, cholelithiasis, and a small right kidney. Laboratory results were as follows: serum calcium 2.82 mmol per liter (11.3 mg per dl), albumin 27 grams per liter (2.7 grams per dl), urea nitrogen 11.42 mmol per liter (32 mg per dl), and creatinine 184 μmol per liter (2.2 mg per dl). Flexible sigmoidoscopy, barium enema, esophagogastroduodenoscopy, and bone scan showed no evidence of malignancy. Tests for carcinoembryonic antigen, prostate-specific antigen, and serum protein electrophoresis revealed no abnormalities.

The patient had a history of hypertension that was well controlled with the use of atenolol, abdominal aortic aneurysm repair five years previously, and persistent edema of both wrists and hands for five years. He had a 70-pack-year history of cigarette smoking.

On admission to hospital the patient appeared chronically ill and cachectic. Physical examination revealed extensive skin lesions and bilateral nonpitting edema of the hands. No ophthalmologic abnormalities were detected. Many annular,

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polycyclic, and dermally infiltrative lesions, 2 cm to 6 cm in diameter, were scattered over the back, chest, upper arms, and thighs (Figure 1). They were erythematous and minimally elevated, with palpable areas of central clearing. Older lesions appeared to have a hyperpigmented edge with mild superficial desquamation. The mucosa was not involved.

Figure 1.—Widespread erythematous annular lesions with central clearing are clearly visible.

Abnormal laboratory data were as follows: serum urea nitrogen 16.07 mmol per liter (45 mg per dl), creatinine 282 μmol per liter (3.2 mg per dl), calcium 3.49 mmol per liter (14.0 mg per dl), phosphorus 1.81 mmol per liter (5.6 mg per dl), albumin 31 grams per liter (3.1 grams per dl), aspartate aminotransferase 1.35 μkat per liter (81 IU per liter), and alkaline phosphatase 1.92 μkat per liter (115 IU per liter). Urinalysis showed 1+ calcium oxalate crystals and no protein, bacteria, or cellular elements. The electrocardiogram revealed no serious abnormalities and a normal QT interval.

The chest roentgenogram showed mild bilateral diffuse perihilar interstitial infiltrates in a reticular pattern without adenopathy. Computed tomography of the chest and abdomen revealed minimal bullous disease in the apex of the right lung, a small calcified granuloma in the left upper lobe of the lung, a few scattered calcified splenic granulomas in the spleen, and atrophy of the right kidney.

Therapy was begun with vigorous intravenous saline hydration and furosemide diuresis. Prednisone, 20 mg per day orally, and a three-day course of etidronate sodium, 325 mg per day intravenously, were then added to the regimen.

Additional laboratory results were as follows: intact parathyroid hormone level determined by immunoradiometric assay was less than 0.2 pmol per liter (normal < 1.5), parathyroid hormone-related peptide was undetectable, human immunodeficiency virus antibody test was negative, serum angiotensin-converting enzyme level was 158 U per liter (normal range 8 to 52), and 1,25-dihydroxyvitamin D level was 130 pmol per liter (normal range, 36 to 120). Purified protein derivative and control tests were nonreactive.

A skin biopsy showed many noncaseating granulomas in the dermis and subcutaneous tissue (Figure 2). Special stains for fungal and acid-fast organisms were negative. A bone marrow biopsy showed no abnormalities.

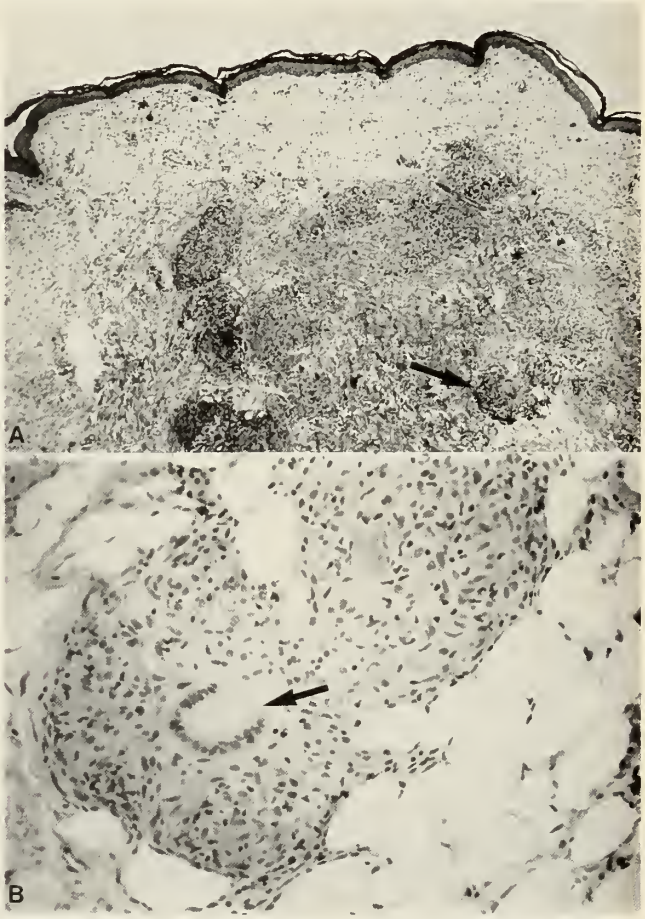

Figure 2.—**A,** Photomicrograph of the skin biopsy specimen shows many noncaseating granulomas **(arrow)** throughout the dermis consistent with sarcoid (original magnification × 100). **B,** Magnified view shows a sarcoid granuloma with multinucleated giant cells **(arrow),** epithelioid histiocytes, and admixed lymphocytes (original magnification × 400).

The patient remained afebrile and had increased strength and return of appetite. Serum calcium and creatinine levels decreased to 2.67 mmol per liter (10.7 mg per dl) and 185 μmol per liter (2.1 mg per dl), respectively. The patient was discharged from the hospital on a regimen of prednisone, 40 mg per day orally, and etidronate, 1 gram per day orally. A diagnosis of sarcoidosis was considered probable.

Three weeks later, the patient had regained 4.5 kg (10 lb) and there was generalized clearing of the skin lesions, particularly on the back. Serum calcium, creatinine, and 1,25-dihydroxyvitamin D levels were within normal limits. Etidronate therapy was discontinued, and gradual withdrawal from prednisone was begun.

Discussion

Sarcoidosis may involve any organ but commonly affects the lungs, eyes, mucous membranes, skin, liver, spleen,

musculoskeletal system, and heart. The diagnosis is established by compatible clinicoradiographic findings supported by histologic evidence of widespread epithelioid cell granulomas, preferably in more than one organ.

In a worldwide review of 3,676 patients with sarcoidosis, 68% of patients were under 40 years of age when first seen, and 80% had evidence of hilar lymphadenopathy.[2] Constitutional symptoms may occur in more than a third of patients; weight loss, fatigue, and fever are the most common.[3]

As many as a third of patients with sarcoidosis have ocular inflammatory disease, and the sudden onset of redness, photophobia, and blurred vision are often the presenting features.[4] In a university-based population, 5.5% of patients with uveitis had associated systemic sarcoidosis.[5] The most frequent manifestation is anterior uveitis, but patients may rarely have isolated posterior uveitis, optic nerve inflammation, or orbital disease.[4] Vigorous therapy with topical or systemic corticosteroids should be initiated to prevent the complications of glaucoma and blindness.

Persistent hypercalcemia is observed in only 2% of patients with sarcoidosis and is usually associated with severe and widespread disease.[6] It represents one of the firm indications for steroid therapy because of the risk of renal impairment, nephrocalcinosis, and nephrolithiasis.[7] Renal dysfunction resulting solely from granulomatous infiltration is rare. Hypercalcemia can depress the glomerular filtration rate directly.[8]

The presumed mechanism of hypercalcemia is the extrarenal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by macrophages in sarcoid granulomas.[9-11] This results in the overproduction of 1,25-dihydroxyvitamin D, which augments calcium absorption by the gastrointestinal tract.[12] Administration of low doses of corticosteroids generally causes prompt reduction of the circulating level of 1,25-dihydroxyvitamin D and return of the serum level of calcium to the normal range.[13]

Therefore, the level of 1,25-dihydroxyvitamin D is often elevated and the level of parathyroid hormone is almost always suppressed in patients with sarcoid-related hypercalcemia. This is in contrast to the substantially reduced level of 1,25-dihydroxyvitamin D in patients with hypercalcemia resulting from malignancy.[14]

Cutaneous manifestations of sarcoidosis vary widely.[15-18] The lesions are usually asymptomatic but may rarely be pruritic.[19] The presence of cutaneous manifestations is often important because a skin biopsy may establish the diagnosis in unsuspected cases.

Nonspecific lesions represent hypersensitivity reactions without granulomas. The most common is erythema nodosum, found in 17% of sarcoid patients worldwide.[2] Erythema multiforme is rarely seen.

Specific lesions, found in 9% of sarcoid patients worldwide,[2] have characteristic histologic findings with noncaseating granulomas. Common lesions include lupus pernio, persistent plaques, papules, subcutaneous nodules, scar infiltrates, and mucous membrane lesions.

Lupus pernio consists of violaceous and often large and disfiguring plaques or thickenings that can involve the nose, cheeks, earlobes, fingers, and knees. Persistent plaques are usually large, purplish brown, dark, and nontender lesions. They are commonly located on the limbs, buttocks, and abdomen and can have irregular, annular, or serpiginous shapes. Papules may erupt suddenly and appear in crops scattered over the face and limbs. Mucous membrane lesions are small and involve the mouth and conjunctivae.

Other uncommon or rare variants include skin ulcerations,[20] nonscarring alopecia,[21] and erythema multiforme-like target lesions.[22] Hypopigmented macules, ichthyosiform, and psoriasiform lesions are also uncommon and usually present in African-American patients.[23]

Erythrodermic or widespread erythematous lesions have rarely been described; most are minimally infiltrative and coalesce into sheets of dermatitis.[21,24] The lesions in this patient clinically resembled a deep gyrate erythema, which are deep dermal nongranulomatous lesions of unknown cause.[25] They also can form rings with indurated borders and central clearing but are often migratory with rapidly advancing edges. These lesions also lacked the characteristic wood grain appearance of erythema gyratum repens, which is often associated with underlying malignancy.

The differential diagnosis of annular sarcoidosis should also include tuberculoid leprosy, granuloma annulare, tertiary syphilis, lupus erythematosus, and lymphoma cutis.[18]

My patient's lesions were unusual in that they cleared so rapidly in response to therapy. Sarcoid plaques are typically slow to resolve and are often resistant to therapy.[15-18]

Summary

Sarcoidosis is a multisystem disease that often presents with constitutional symptoms and ocular and skin manifestations. The chest roentgenogram may show no abnormalities or only diffuse interstitial disease. The serum calcium level is uncommonly persistently elevated and responds rapidly to low-dose corticosteroid therapy. The level of 1,25-dihydroxyvitamin D is often elevated, and the level of parathyroid hormone is almost always suppressed. Skin manifestations vary considerably and may appear in an unusual fashion. A skin biopsy may often be essential in the diagnosis of sarcoidosis.

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Primary Biliary Cirrhosis and Adult Celiac Disease

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OVERLAPPING SIGNS and symptoms of two relatively rare disorders, celiac disease and primary biliary cirrhosis (PBC), may result in delays in establishing the diagnosis of both conditions. In a patient with diagnosed celiac disease, persistently abnormal results of liver function tests after symptomatic improvement on a gluten-free diet should arouse suspicion of primary liver disease.

Report of a Case

The patient, a 59-year-old airline pilot, was seen in September 1988 because of persistently abnormal results of liver function tests dating to 1980 and with the chief complaint of intermittent diarrhea and weight loss of 18 months' duration. The patient had 8 to 20 pale, foul-smelling, nonbloody bowel movements daily associated with bloating after meals and borborygmi. On occasion the diarrhea occurred during the night and had not been associated with abdominal discomfort. Despite what the patient perceived as an adequate dietary intake, he had lost about 9 kg (20 lb) during the first six months of his diarrhea. His weight had been relatively stable for a year since then. There had been no fevers, pruritus, or abdominal pain. He did not use laxatives, and he had not traveled outside of the country. He had not had exposure to water suspected of harboring *Giardia* species, nor had he received antibiotics in the past several years.

His medical history was unremarkable other than having persistently abnormal liver function for six years. He had not had previous abdominal operations or radiation exposure. He took no medications other than occasional vitamins, and there was no notable history of alcohol use. He had been a ten pack-year smoker. There was no family history of gastrointestinal diseases. There were no symptoms suggestive of extraintestinal manifestations of inflammatory bowel disease.

On physical examination, he was afebrile, weighed 79 kg (174 lb), was 177 cm (5 ft 10 in) tall, and had no skin stigmata of end-stage liver disease. His abdomen was nontender, and there was no evidence of organomegaly. His stool was pale, grossly fatty, and negative for occult blood. A sigmoidoscopic examination was unremarkable, as was histologic evaluation of rectosigmoid mucosal biopsies. Stool culture and ova and parasite studies were negative. The hemoglobin level was 132 grams per liter (13.2 grams per dl).

Laboratory data since 1982 were reviewed. His alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels had been elevated during that time, minimally at first and gradually rising thereafter (Table 1). The serum bilirubin value was normal. An upper gastrointestinal x-ray study with small bowel follow-through revealed coarsening of duodenal folds, some narrowing of the descending duodenum, and dilatation of the small bowel with a mucosal pattern compatible with sprue. Upper gut endoscopy was then done. Excellent-quality biopsy specimens of small intestine were obtained, revealing total villous atrophy with glandular crypt hyperplasia and intraepithelial lymphocytes consistent with celiac disease (Figure 1). The patient was placed on a gluten-free diet, and his steatorrhea resolved shortly thereafter. His weight had increased 3.2 kg (7 lb), and his subjective feeling of strength was increased. Examination of his stool showed no evidence of fat.

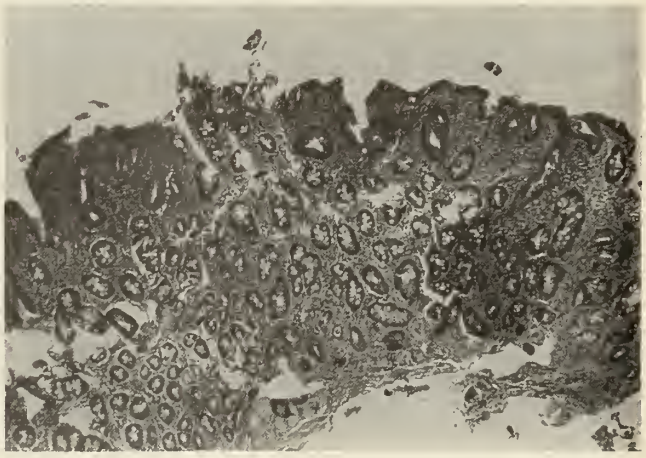

Figure 1.—The small intestine mucosal biopsy shows total villous atrophy. The mucosal glandular crypts have a hyperplastic appearance and are elongated. The lamina propria contains an increased amount of chronic inflammatory cells with an increased number of intraepithelial lymphocytes at the absorptive surface (hematoxylin and eosin stain; original magnification × 25).

The results of follow-up liver function tests initially were nearly normal in 1989 as well. Despite the resolution of his steatorrhea and gradually increasing body weight, however, liver function test levels began to rise thereafter. In January 1990 his alkaline phosphatase level was 442 units per liter. An antimitochondrial antibody test was positive at a dilution of 1:4,096 (normal <1:40). His antismooth muscle antibody test was trace positive at a dilution of 1:64 (normal <1:40). A needle liver biopsy was done a month later that showed findings of primary biliary cirrhosis (Figure 2) and precirrhotic bridging fibrosis (Figure 3). The liver biopsy showed no evidence of sclerosing cholangitis. At that time

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
AST = aspartate aminotransferase
PBC = primary biliary cirrhosis

his immunoglobulin M level was 3.29 grams per liter (329 mg per dl) (normal 0.40 to 2.50). Antinuclear antibody, serum copper, and ceruloplasmin levels were normal. Alkaline phosphatase isoenzyme measurements revealed an increased liver fraction. Endoscopic retrograde cholangiopancreatography was not done because of the lack of evidence for cholangitis or inflammatory bowel disease.

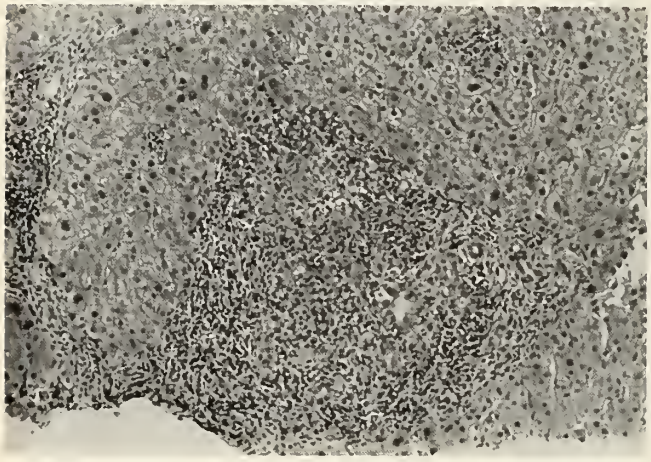

Figure 2.—A liver needle biopsy shows enlargement of the portal area with a prominent epithelioid granuloma. There is an increased number of lymphocytes that impinge on bile ducts and show evidence of glandular destruction. There is no evidence of cholangitis (hematoxylin and eosin; original magnification × 100).

In February 1990, he was placed on a regimen of ursodeoxycholic acid in a dose of 300 mg twice a day in the hope of preventing cirrhosis. Follow-up laboratory data two months later revealed improvement of his liver function test results (Table 1). His alkaline phosphatase level had dropped to 253 units per liter, and his AST and ALT levels were only minimally elevated at 41 and 46 units per liter, respectively. He continues to feel well without evidence of pruritus or other symptoms referable to hepatic dysfunction. Follow-up small bowel and liver biopsies have not been performed to date.

Discussion

Since 1978, there have been 20 case reports of patients—15 female and 5 male—with both celiac disease and PBC.[1-12] Three of these cases were described in letters to the editor.[2,3,10] Once patients were placed on a gluten-free diet—

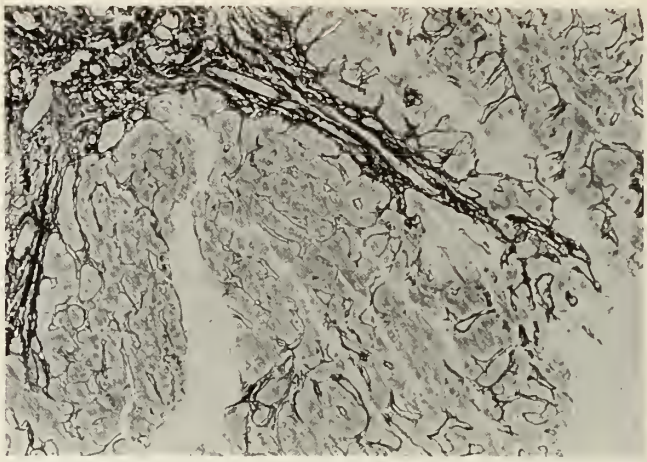

Figure 3.—A reticulin stain of a liver needle biopsy shows moderate portal fibrosis. There is extension of reticulin fibrosis along lobular margins with portal-to-portal bridging (original magnification × 100).

reported in 11 patients[1,5,8,11]—their diarrhea usually resolved but the results of liver function tests remained unchanged. In one patient, pruritus developed after small bowel mucosal damage healed.[1] The effect of a gluten-free diet on liver function test results in three cases was not reported.[2-4] Olsson and co-workers reported that of 26 consecutive patients with PBC, 5 had intestinal villous atrophy.[5] Three of these five patients were male. Four had positive antismooth muscle antibody tests, and one was positive for antinuclear antibody. HLA-B8 was present in three.

A case of celiac disease was reported in a 69-year-old man who had a history of PBC followed by dermatitis herpetiformis.[8] After a year on a gluten-free diet, the jejunal biopsy appearance had almost returned to normal and the skin problems had almost completely disappeared. In a study of the prevalence of PBC in a Swedish population, two patients were found to also have celiac disease complicated by osteomalacia.[9] In 1986, a case of celiac disease and PBC was reported in a woman who had presented initially with diarrhea that responded to a gluten-free diet, but her liver function test results did not return to normal.[11] Seven years later, ascites, jaundice, and hepatosplenomegaly developed. A postmortem liver biopsy showed PBC. The most recent case of PBC and celiac disease was in a woman who was also found to have renal tubular acidosis in association with Sjögren's syndrome.[12]

Primary biliary cirrhosis is a rare chronic disease of unknown etiology, primarily affecting middle-aged women, that is characterized by inflammation and necrosis of intrahepatic bile ducts.[13] It may be associated with autoimmune syndromes—Sjögren's syndrome, seronegative arthritis, progressive systemic sclerosis, and thyroiditis.[12] Its onset is

TABLE 1.—*Historical Laboratory Data*

Serum Laboratory Test	*1982*	*1985*	*1988*	*1989 Feb/July*		*1990 Jan/Apr*	
Aspartate aminotransferase, units/liter*	76	54	128	69	64	113	41
Alanine aminotransferase, units/liter*	135	83	144	90	101	133	46
Serum alkaline phosphatase, units/liter†	152	158	422	228	329	422	253
Serum total bilirubin, μmol/liter (mg/dl)‡	7 (0.4)	7 (0.4)	12 (0.7)	--	--	10 (0.6)	--

*Reference range, <40 units/liter.
†Reference range, 35 to 65 units/liter.
‡Reference range, 0 to 26 μmol/liter (0.0 to 1.5 mg/dl).

usually insidious. Asymptomatic patients without physical abnormalities are often diagnosed on the basis of laboratory abnormalities alone.[14] Malabsorption may occur, which has been shown to be due to intraluminal bile acid deficiency.[15] Pruritus and skin pigmentation are considerably less prominent in men initially, but survival is similar among men and women.[16]

Celiac disease is a rare disease of the small intestine that is characterized by villous atrophy of the cryptic hyperplastic type and malabsorption. It is caused by hypersensitivity to cereal, grains, and storage proteins (gluten or a substance derived from gluten, gliadin) found in wheat, barley, and rye. Celiac disease generally occurs either as a disease limited to the gastrointestinal tract or in conjunction with dermatitis herpetiformis.[8] It has also been associated with autoimmune diseases, including thyrotoxicosis, diabetes mellitus, fibrosing alveolitis, and chronic active hepatitis.[17]

Liver function disturbances in adult patients with celiac disease are not unusual and are generally thought due to nonspecific reactive hepatitis or fatty infiltration. Moreover, osteomalacia resulting from malabsorption may cause elevated alkaline phosphatase levels. An association of primary sclerosing cholangitis and celiac disease was noted in three men who had chronic cholestatic liver disease that led to endoscopic cholangiopancreatography; these men had fibrous or inflammatory cholangitis on liver biopsy.[18] Hagander and colleagues found nonspecific histologic evidence of liver injury in 16% and abnormal results on liver function tests in 39% of patients with celiac disease.[19] Elevated aminotransferase activities usually decreased substantially after a gluten-free diet was instituted. In theory, nonspecific morphologic hepatic changes should resolve once a patient is treated.

Behr and Barnert discussed current theories regarding a common cause of PBC and celiac disease.[11] One theory concerns the formation of immune complexes with a common antigenic basis, which mediate tissue damage. To date, however, no specific antigen has been identified nor is there general acceptance that PBC is an immune complex disease. A second theory postulates a diminished function of suppressor T cells in patients with PBC and celiac disease, which permits effector cytotoxic lymphocytes to attack a modifying antigen, that is, gluten.[20] These effector cells would recognize and attack a patient's own histocompatibility antigens. This theory requires that the recognized antigens are either present in high concentration in biliary epithelial cells or that they are modified in some way.[21]

The case reports outlined here suggest that concomitant celiac disease and PBC may occur more often in men than would be expected based on the incidence of PBC in men. The eventual occurrence of both disorders may be more common than is generally realized, if patients are tested carefully and observed for a long enough period of time. We recommend for patients with either of these two diseases that they be observed not only to assess their condition and response to treatment of the recognized problem, but also to look for signs and symptoms of the other disease. In particular, patients with intestinal malabsorption due to celiac disease should have periodic liver enzyme tests because persistent abnormal results may be the only clinical manifestation of liver disease.

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Commentary

On Sale: Future Health Care
The Paradox of Discounting

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INTEREST IN stemming the increasing costs of medical practice has led to the proliferation of cost-effectiveness research. The results of this research, as implemented in practice guidelines or reimbursement plans, will likely have a profound effect on the practice of medicine. Discounting, a concept with roots in economic theory, is an essential element of cost-effectiveness research. Although of key importance in this research, discounting can result in a series of apparent paradoxes. To improve their ability to interpret the results of cost-effectiveness research, it is important for clinicians to understand the principles of discounting. These principles and the apparent paradoxes as they apply to clinical practice are reviewed.

A) Many effective prevention programs are not cost effective.

B) The health effects of future venereal disease are unimportant when considering the overall health effects of neonatal circumcision.

C) Preventing penis cancer with circumcision costs money, diminishes health, and is probably not cost effective.

D) Preventing penis cancer with circumcision saves money, improves health, and is probably cost effective.

These are true statements, yet they seem either counterintuitive (A and B) or contradictory (C and D). These are important statements because they are similar to those made in health policy research. Every practitioner should be aware that this type of statement will mold the future practice of medicine through practice guidelines and third-party reimbursement practices.

There is a trend towards the development of practice guidelines. For example, in 1981 the American College of Physicians published a review of four authors' prevention guidelines.[1] In 1991 Hayward and colleagues published a similar article, but this more recent review included prevention guidelines from 23 authors on more than 50 interventions.[2]

There is also a growing trend towards government intervention in the spiraling costs of health care. One method is to ration care by evaluating the relative cost effectiveness of various strategies and funding those programs that offer the greatest health impact for the health care dollar. This type of explicit rationing has received much attention. For example, in Oregon the Robert Wood Johnson Foundation funded the Oregon Health Priorities for the 1990s project to determine which health services the citizens of Oregon considered the most important (should have the highest priority) for government funding.[3] More recently, the Health Care Financing Administration announced that both costs and outcomes will be assessed when considering future medical reimbursement policies. Articles expounding the fears of inequities induced by such rationing followed these announcements.[4-6]

The operative phrase is cost effectiveness, a term that has many meanings.[7] From the health policy perspective, cost effectiveness usually means cost saving or that the health outcomes justify the costs. In both cases economic analysis plays a crucial role. For this reason economic theories, through their role in cost-effectiveness research, affect health policy and practice guidelines formulation.

As illustrated in sentences A to D, a problem surfaces because the psychology used in a cost-effectiveness analysis seems either inconsistent or contradictory. Apparently a paradox results when the psychology of decision making is implemented in economic analyses. In this article we examine the paradox, evaluate its effect on health policy research, and explore topics for future research.

Psychology

Your employer calls you in and tells you that you have done well this year, keeping costs down and increasing productivity, and that you deserve a bonus. He tells you that your bonus is $10,000 and that you can decide how you get it. He pulls out ten $1,000 bills and gives you the option of taking these now or coming back in a year and receiving the $10,000 adjusted for inflation. You calculate that if inflation is 5% this coming year, you will get $10,500. Which would you choose?

Most people have a positive time preference with regard to money. This means that most would rather have the $10,000 in their pocket today than in a year, even after adjusting for inflation. There are many reasons for this.[8,9(p316),10-14] First, the money could be invested and earn more than inflation. Second, the money in hand can be spent today, allowing you to enjoy the benefits of the dollars now rather than in the future. Third, many people do not trust the future. This may be because they are not sure they will be alive in a year and they want the money now while they can enjoy it. Also, the source of the $10,000 may default on the dollars owed. The second and third factors indicate that our preference for today's dollar is not simply a matter of its investment potential. Thus, the interest rate is probably the lower limit of the monetary discount rate. It is important to emphasize that discounting is *not* designed to adjust for inflation.[8] Rather, it is based on multifactorial preferences for present over future dollars.

Economics

This positive time preference for money has an interesting corollary, one that leads to the paradox just mentioned. If you prefer $10,000 today to an inflation-adjusted $10,000 in the future, then you do not value the future dollar as much as the present dollar. This has nothing to do with inflation; the preference holds even after adjusting for inflation. Based on this preference, economists conclude that when future dollars are compared with present dollars in an economic analysis, the future dollars must be discounted. Discounting is the

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quantitative process of adjusting, usually by decreasing, the value of a future outcome (such as dollars) to its present value.

Discounting is not an esoteric topic but is a central element of cost-effectiveness analysis. For this reason discounting affects health policy formulation and clinical practice. The importance of discounting and its related issues is emphasized in publications from the Institute of Medicine,[15] the Office of Technology Assessment,[16] important textbooks in the field,[8,9] and classic articles in the literature.[17,18] A recent review of articles published in five journals, including THE WESTERN JOURNAL OF MEDICINE, shows that more than 70% of articles on cost effectiveness appropriately used discounting.[19] In addition, discounting played a central role in many articles referenced by the US Preventive Services Task Force.[20] Finally, discounting is an essential element of the quantitative method used by many authors of practice guidelines. Variations in this methodology may explain the conflicting guidelines from different authors.[1]

Basics of Discounting

The process of calculating the present value of future dollars by discounting is mathematically the opposite of calculating the future value of present dollars with interest. For example, \$100 invested at 5% interest will be worth \$105 (\$100 + [0.05 × \$100]) after one year. In contrast, if the discount rate is 5%, then \$100 a year from now is currently valued at \$95 (\$100 − [0.05 × \$100]). The relationship between interest and discounting is further demonstrated by the formulas for calculating the various rates. Formula 1 is the discount rate equation and is used to calculate the discount multiplier (the number that adjusts for the discount rate) for some time in the future. Formula 2 is the compound interest rate formula. The discount rate over several years is approximated by the mean of the discount rate for each year. In the following formulas, d is the discount rate, i is the interest rate, and t is time, usually in years:

(1) Discount multiplier at time $t = \dfrac{1}{(1+d)^t}$

(2) Interest multiplier at time $t = (1+i)^t$

Just as compound interest offers dramatic returns after a few years, the compounded effects of discounting can have a marked influence on an economic analysis. Table 1 and Figure 1 illustrate the effect of discounting. For example, the discount multipliers for 25 years at 5% and 10% discount rates are, respectively, 0.578 and 0.381. Thus, if a person earns an inflation-adjusted \$20,000 a year for 25 years, the total inflation-adjusted earnings will be \$500,000. Applying a 5% discount rate reduces the present value of those earnings to 0.578 × \$500,000 = \$289,000. A 10% discount rate reduces the present value of earnings to 0.381 × \$500,000 = \$190,500. The present value, after discounting, of the inflation-adjusted \$20,000 earned in the 25th year is 0.295 × \$20,000 = \$5,900 at a 5% discount rate and only 0.092 × \$20,000 = \$1,840 at a 10% rate.

TABLE 1.—*Discount Multipliers for Various Years at 5% and 10% Discount Rates*

	5% Discount Rate		10% Discount Rate	
Years = n	*n^{th} yr*	*Average of Present to n^{th} yr*	*n^{th} yr*	*Average of Present to n^{th} yr*
1	0.952	0.976	0.909	0.954
2	0.907	0.953	0.826	0.910
3	0.864	0.930	0.751	0.870
4	0.823	0.908	0.683	0.831
5	0.784	0.887	0.621	0.795
10	0.614	0.791	0.386	0.645
15	0.481	0.709	0.239	0.532
20	0.377	0.639	0.149	0.447
25	0.295	0.578	0.092	0.381
30	0.231	0.525	0.057	0.330
40	0.142	0.440	0.022	0.257

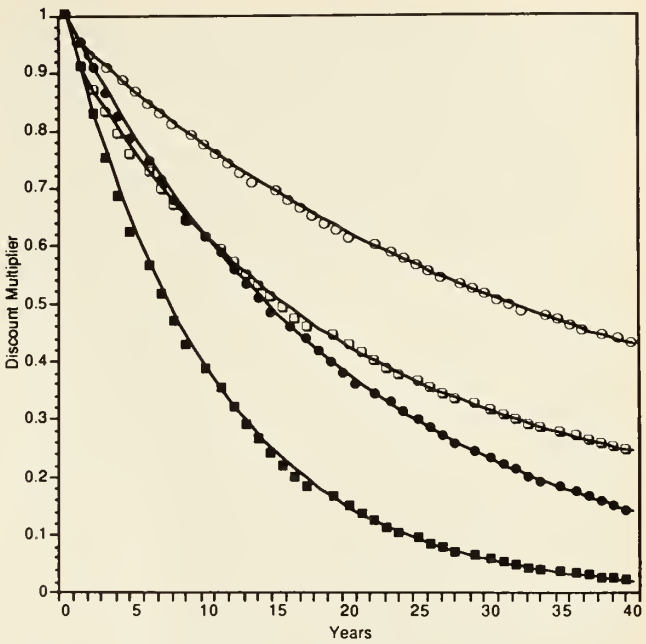

Figure 1.—Discount multipliers for 5% and 10% discount rates from the present to 40 years. ● = 5% discount rate in n^{th} year, ○ = 5% discount rate averaged from present to n^{th} year, ■ = 10% discount rate in n^{th} year, □ = 10% discount rate averaged from present to n^{th} year.

Economists, although comfortable with the concept of discounting, do not agree on the discount rate.[8,10] In cost-effectiveness research, proposed discount rates vary from 2% to 20%, including a 0% calculation in the sensitivity analysis.[8,10,21,22(p70)] Typically, we assume that the discount rate is the rate of interest earned by today's investments. As mentioned, this is probably a low estimate.

In cost-effectiveness research, the net dollar cost of a program is divided by the net health effect. The numerator of the cost-effectiveness ratio is therefore simply the result of an economic analysis, and the net future dollar cost should be discounted as in any economic analysis. Discounting future health effects, on the other hand, is an area of intense controversy. In part there may be a hesitancy to treat health in the same manner as dollars. Health, it may be argued, should be on a higher level than dollars, and to discount health in the same way as one would discount dollars in some way diminishes the value of life. On the other hand, discounting does not imply that the future dollar (or health outcome) will be in itself less important or valuable. Instead, discounting simply considers today's valuation of future wealth or health.

Paradox Revisited

In sentence A, prevention programs are not cost effective. Although this is not the case for all prevention pro-

grams, it is a major obstacle to getting federal funding for preventive care. Prevention programs incur a bulk of their dollar costs today, but their economic and health benefits occur in the future. Discounting these future benefits puts the program at a disadvantage.

Discounting also plays a role in paradox B, that future venereal disease is not an important rationale for circumcision. Assume that 10% of men will get a venereal disease at an average age of 20 years. Further assume that the symptoms of this venereal disease will last two weeks. The discount multiplier for 20 years at 5% is 0.377 and at 10% is 0.149. Given these assumptions, the 2 weeks of symptoms in 20 years are valued today the same as 14 days $\times$ 0.377 = 5.3 days at the 5% rate and 14 days $\times$ 0.149 = 2.1 days at the 10% rate. Because only 10% of men will have the disease, these discounted future effects can be decreased further to 5.3 days $\times$ 0.1 = 0.5 days at 5% and 2.1 days $\times$ 0.1 = 0.2 days at 10%. With most reasonable variations of the base assumptions, the health effects of the future venereal disease are presently valued at only a few hours. This seems hardly a just rationale for circumcision.

Finally, the apparent paradox of statements C and D can be explained through discounting. The dollar costs and the health effects of routine neonatal circumcision occur in both the present and the future. For example, a circumcision done today will incur a charge for the procedure as well as a charge for any possible complications of the procedure. As a result of the circumcision, future health may improve (less penis cancer)[23,24] and the patient will have the potential for a greater earning capacity (if circumcision prevents penis cancer, the patient will be able to remain healthy and continue working). In a recent cost-effectiveness evaluation of circumcision, 1,000 hypothetical infants were circumcised and 1,000 were not.[25] As with any cost-effectiveness analysis, the investigators made a series of assumptions and then tested the strength of these assumptions. One such assumption was that penis cancer occurs in 1 of every 600 uncircumcised adults.[23] The cost effectiveness of circumcision was calculated after discounting future dollars at a 5% rate as well as at a 0% (no discounting) rate.

Penis cancer prevention will be a late benefit of circumcision. By discounting future dollars and health, one diminishes the apparent benefits of circumcision. Likewise, by using the 0% discount rate, circumcision is favored. Based on the assumptions in this article, if the cost of penis cancer treatment is $20,000 and if future dollars and health are discounted at 5%, then circumcising those 1,000 infants has a net lifetime cost of $96,658 while losing 1.14 quality-adjusted life years. On the other hand, this same program saves $13,270 and gains 11.05 quality-adjusted life years if discounting is not performed. With discounting, circumcision costs dollars and loses health; without discounting, circumcision saves dollars and gains health.

These are not merely academic exercises. Health policy and practice guidelines are based in part on economic evaluations that use discounting. Discounting can have a dramatic effect on the outcome of such evaluations. For this reason practitioners should be familiar with how discounting affects the cost-effectiveness research.

Resolving the Paradox

Health policy and practice guideline formulation increasingly rely on cost-effectiveness research. This research, therefore, leads to a form of rationing. As a society we resist formal rationing, but physicians have always rationed. Physicians decide that the benefits of the program or procedure will likely justify the costs. For example, there are more patients eligible for dialysis than there are dialysis machines. Physicians must ration dialysis units. Often an intensive care unit fills, and the physician must decide who has the greatest need for the limited number of beds. Many physicians treat urinary tract infections with ampicillin, even though ciprofloxacin hydrochloride is more effective, because the increased effectiveness of ciprofloxacin does not justify its greater cost. During the Persian Gulf War there was a shortage of gamma globulin, and physicians had to decide not who needed it but who needed it the most.

Rationing per se is not the problem, but some health policy research does lead to conclusions that we, as a society, may not choose to accept. Do we want to live with a discounting-induced paradox? For example, do we want to withhold funding from prevention programs because we discount future health benefits? Although the paradox was caused in part by discounting, the answer may well rest with discounting. Traditionally, both future dollars and future health are discounted, but is this justified? Do most people really prefer present health to future health? Does prognosis or age make a difference? Does the type of program (preventive versus curative) matter? Does the risk of the program affect the discount rate?

The fact that there is an apparent paradox does not mean that the cost-effectiveness model is wrong, nor does it mean that we should stop discounting future outcomes. The paradox is likely caused by the relative youth of this field of research and begs for more research into discounting, preferences, and decision making.

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First World Exports to the Third World—Capital, Technology, Hazardous Waste, and Working Conditions—Who Wins?

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THE INDUSTRIALIZED NATIONS of the world have exported vast quantities of hazardous waste and numerous hazardous industries to Third World countries. The United Nations Environment Programme (UNEP) and the Organization for Economic Co-operation and Development (OECD) estimate that as much as 20% of global industrial waste is transported to other countries. This relatively new social problem represents at least 30 million tons of waste per year.[1] Foreign companies and investors have provided 60% of all industrial investment in developing countries over the past decade.[2] For many nations such investment is the primary source of new jobs.

These activities have created a critical situation in much of the Third World. What has brought about this threat to worker health and to the world's environment? Three conditions are primarily responsible: the increasing restrictions and fines in industrialized nations related to the manufacture of hazardous products; the high cost and difficulty of handling and disposing of hazardous wastes at home; and the lower cost of labor in Third World countries and the lack of regulations protecting workers and the environment.

Developing countries, for the most part, have few enforceable regulations. They are concerned with overwhelming problems of unemployment, malnutrition, and infectious diseases, often to the exclusion of environmental hazards. Newly industrialized countries are eager for the financial benefits that foreign companies and foreign investors bring them. With those benefits, however, come social and ecologic problems. Unfortunately, most industrialized nations, including the United States, do not have environmental laws with provisions that apply abroad.[3]

Consequently, Third World cities in areas favored by migrating industry are faced with severe air pollution, inadequate sewage treatment and water purification, and rampant dumping of toxic wastes on or in the ground or in waterways. All residents are affected by the deteriorating environment in the Third World, but workers in the rapidly expanding industries have additional serious concerns. They have flooded into these areas seeking jobs promised by the foreign companies. When they arrive, they find that housing is inadequate or nonexistent, and they and their families must live in huts, sleeping on the ground, without safe water, in places far removed from medical care.[4]

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Occupational Effects

In most Third World countries, workers have limited education, skills, and training. They are overseen by employers with limited financial resources who are primarily concerned with low-cost production. The workplace may be unsafe, in older buildings, and with machinery lacking safety devices. In many countries, workers have never been given protective clothing, safety glasses, or respiratory or hearing protection. Inspections by health and safety agencies, if they exist, are rare because of long travel distances and limited personnel and funds. Consequently, worker fatality rates are much higher in newly industrialized countries than in the developed nations, and injuries in the workplace occur with rates common to the developed nations during the early years of the industrial revolution.[5] In this regard, the industrial revolution is taking place all over again, but with much larger populations of workers and in many more countries.

An estimated 30% of the urban population of developing countries make up what is called the informal sector of workers engaged in building or self-employed carpentry, domestic service, selling crafts to tourists, prostitution, and a variety of criminal activities such as smuggling and drug sales.[6] To this number must be added the large numbers of children subjected to daily labor all over the world. Even the home in developing countries can be the site of industrial activities from crafts production to electronics assembly. Organization of labor is unlikely with this group of workers because they are often very young or very old. Government programs of workers' compensation for injuries and illnesses seldom exist for the informal sector.

Foreign companies entering a Third World country generally accept the lower levels of safety and health standards of the host country, if such even exist. Consequently, work-incurred injuries and illnesses are much more frequent in these countries than they are in industrialized nations.[7] Despite the difficulties encountered in the workplace, the flow of workers will increase in developing countries as the number of young workers swells from 2 billion to 3.5 billion by the year 2025 ("Pollution in Asia: More People, Bigger Cities, Greater Wealth, Worse Filth," *The Economist*, October 6, 1990, pp 25-28). Competition for jobs will also increase, and as a result worker demands for improved working conditions will probably not be voiced.

Environmental and Health Effects

The incidence of environmental and occupational disease worldwide is higher than it has ever been in recorded history. The United Nations estimates that 6 million cases of occupational disease occur each year, most of them in Third World countries.

In China, for example, 1 million people have silicosis from occupational exposure to dust. Although silicosis is rare

ABBREVIATIONS USED IN TEXT

ILO = International Labour Office
OECD = Organization for Economic Co-operation and Development
UNEP = United Nations Environment Programme
WHO = World Health Organization

in industrialized countries and is entirely preventable, it is the most common occupational disease in China, which has the world's largest population. In some Third World countries, asbestosis is the major occupational disease among miners, construction workers, and asbestos workers. Yet, the Canadian asbestos industry promotes the use of asbestos in developing countries where the demand for low-cost building materials outweighs health concerns (J. Dahl, "Canada Encourages Mining of Asbestos, Sells to Third World," *Wall Street Journal,* September 12, 1989). The Canadian government has supported its industry by sending free samples of asbestos to any country where future manufacturing of asbestos products is a possibility.

Lead poisoning is of epidemic proportions in many developing countries. In Malaysia, for example, blood levels of lead in many lead-acid battery workers is three times higher than allowed in US workers.[8] Lead in the air of Ahmadabad, India, is sufficient to cause an increase of 12 to 28 μg per dl in blood levels of lead depending on the time of year. Air levels are much higher in Columbo, Sri Lanka.[9] Blood levels of lead in an urban area of Pakistan range from 52 to 102 μg per dl.[10] Most developing countries still rely on lead pipes to convey drinking water. Lead is also a problem in unlabeled cosmetics and other consumer goods, and some traditional medicines contain high levels of lead.[11]

The manufacture and use of pesticides is increasing rapidly in Third World countries. They are often manufactured by foreign-owned companies or local companies financed by foreign interests. Pesticides, such as dichlorodiphenyltrichloroethane (DDT) and 1,2-dibromo-3-chloropropane (DBCP), which are banned in most developed nations, are widely sold and used without restrictions in the Third World. When health hazards cause the removal of a pesticide from the US market, its export to developing countries often increases. For example, the insecticides chlordane and heptachlor were banned for agricultural uses in the United States in the 1970s. Yet between 1987 and 1989, the US manufacturer produced and exported nearly 5 million pounds of these insecticides to some 25 countries.[12] A partial result of widespread misuse of pesticides in the Third World is a reported 3 million poisonings in Southeast Asia alone and 200,000 deaths, many of which local governments often attribute to suicide.[7] Unfortunately, foreign companies can manufacture any hazardous products as long as they are not forbidden by the host country.

Without question, the further export of hazardous waste and environmentally outmoded industrial plants must be stopped, but such a program will require international cooperation.

International Regulatory Efforts

Fortunately, some international environmental organizations are already at work toward achieving this goal. The United Nations Environment Programme has been working with a number of countries to discourage the export of hazardous materials to less developed nations and to introduce plant site requirements for hazardous industries wherever possible. It is developing centers to provide information on hazardous materials worldwide.[13] The World Health Organization and the International Labour Office (ILO) are providing information and assistance to Third World countries concerning occupational health and safety.[14] The difficulty, however, is that most such organizations have severely limited budgets that hamper program development and their ability to fund research in environmental health and in efforts at worker education. The World Medical Association should support WHO/ILO activities, and all medical associations should be increasing their commitments to environmental goals and organizations.

Efforts are also being made to control corporate behavior. Toward this end, the following have attempted to provide a framework for ethical behavior: the OECD Guidelines for Multinational Enterprises, the UN Code of Conduct on Transnational Corporations, and the ILO Tripartite Declaration of Principles Concerning Multinational Enterprises and Social Policy.[2,15,16]

An extremely forceful message must be sent to most industries and nations. This need is indicated by the failure to achieve widespread international support for the findings of the Basel Convention on Transboundary Movements of Hazardous Wastes and Their Disposal.[17] The message that industrialized nations and their companies are damaging the world's environment and affecting the health of its people can be conveyed with appropriate credibility and force by physicians.

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Editorials

Genetic Heterogeneity and Clinical Disease

THE CORRECT CLASSIFICATION of a hereditary disease is critical for the study of its pathogenesis. It is particularly important to evaluate genetic diseases clinically because each distinct clinical subtype may correspond to a particular mutation or limited set of mutations in the human genome. If a simple relationship can be shown between a mutation (the genotype) and the resulting clinical pattern of disease (the phenotype), early prediction of prognosis becomes possible based on analysis of deoxyribonucleic acid (DNA) alone. Moreover, different mutations may suggest different mechanisms of disease pathogenesis, which in turn may allow therapies tailored to each disease subtype.

Different mutations may be associated with a phenotype that, at first glance, is uniform (genetic heterogeneity). The mutations may be clustered at a single genetic locus or may even affect different genes. Some diseases are essentially homogeneous: sickle-cell disease in Africa is caused by a single mutation. Other disorders are remarkably heterogeneous—more than 40 mutations have been detected in the *CFTR* gene to produce cystic fibrosis. Although some of these mutations are more commonly associated with the development of pancreatic insufficiency, many *CFTR* mutations produce indistinguishable phenotypes.

In this issue Gardner reviews the evidence for genetic heterogeneity in autosomal dominant polycystic kidney disease, Alport's syndrome, and medullary cystic kidney disease, three common hereditary renal disorders.[1] Careful evaluation of the clinical patterns of these disorders shows that none of them are homogeneous. Evaluation of the pattern of inheritance of the three disorders indicates that they are also genetically inhomogeneous. In the case of autosomal dominant polycystic kidney disease, the mutations in the genes of some families are clearly linked to genetic markers on the short arm of chromosome 16,[2] although the mutated gene has not been cloned. In a minority of families, perhaps 5%, the mutation is not found on chromosome 16.[3] Initial evaluation suggested that the pattern of disease is the same whether the mutation resides on chromosome 16 or elsewhere. More detailed characterization, however, reveals a striking difference in the age of onset of end-stage renal failure in the two groups.[4] The chromosome 16-linked mutations seem to produce a much more severe form of the disease with earlier onset and a higher incidence of hypertension than the non-linked form. Although the overlap in age of onset between the two groups is such that the site of the mutation cannot be used to provide an accurate prediction of the age at which renal replacement therapy will be required, a cautious optimism is warranted in persons who have the nonchromosome 16 form, many of whom will live a normal life span without therapy.

Of the inherited renal diseases, Alport's syndrome is the only one for which a molecular basis has been found.[5,6] In three kindreds from Utah, Barker and co-workers[6] found mutations in the α5(IV) isoform of basement membrane collagen. The gene that encodes this collagen, designated *COL4A5*, is found on the X chromosome, explaining the sex-linked pattern of inheritance frequently observed in Alport's syndrome pedigrees. The availability of a genetic marker for the *COL4A5* gene enables analysis of the correlation between the genotype and phenotype in this clinically heterogeneous disease. Sensorineural deafness, lenticonus, and platelet abnormalities, all of which accompany nephropathy in a subset of patients, are prime areas for study. Certain correlations between the clinical pattern of Alport's syndrome and the associated mutation are already becoming apparent. Antignac recently showed that the presence of esophageal leiomyomas in Alport's syndrome correlates with deletions of *COL4A5* that extend upstream of the gene (C. Antignac, MD, INSERM, Paris, oral communication, August 1991). She postulates that these deletions disrupt a second gene or genes upstream of *COL4A5* to produce susceptibility to leiomyomatosis. A small fraction of patients with Alport's syndrome develop antiglomerular basement membrane antibodies after heterologous renal transplantation. Kashtan has evidence that a high proportion of such patients have extensive deletions of the *COL4A5* gene (C. E. Kashtan, MD, University of Minnesota, oral communication, August 1991). Presumably absence of the α5(IV) collagen isoform in the recipient of the graft accounts for the failure to develop immunologic tolerance to this molecule.

In his review Gardner points out that the advent of molecular analysis of genetic disease and the predictive testing that it makes possible have far-reaching ethical implications. The ethical issues in genetic testing are particularly complex for several reasons, but perhaps the most important of these is that the ramifications of a genetic diagnosis go beyond the individual member to the extended family: the diagnosis of polycystic kidney disease in a single at-risk individual often affects dozens of family members, including some who have no close links with the proband. Frequently, even close family members have no idea that they are at risk. The duty of the physician in these instances has not been resolved adequately.[2] Much depends on the nature of the particular disease in question and the benefits (and disadvantages) of diagnosis. The need for research into the use and ethical implications of testing is apparent. The problem is not, however, simply a result of the advent of molecular analysis. After all, in the case of autosomal dominant polycystic kidney disease, for example, presymptomatic diagnosis by excretory urography has been available for decades. Nevertheless, the problem has been brought into focus by the development of tests based on DNA, which are easily performed and, because of their novelty and apparent power, are appealing to patients and their physicians. It is inevitable that their use will grow rapidly. A systematic evaluation of the effects of these tests on individuals and on society as a whole is timely.

Genetic heterogeneity poses a particular problem for tests that are based on genetic linkage (as opposed to direct detection of mutations). Genetic linkage can only be used to make a diagnosis by inference. If there are two forms of the disease, one linked and one unlinked to a particular genetic marker, and if there is no way to distinguish between the two forms, an extensive pedigree analysis is required to confirm linkage to the marker in each family before a reliable diagnosis can be made. This inevitably involves the participation of many family members. Again, the ethical implications of such studies are far reaching. Is a physician entitled to approach the relatives of the patient in order for such a diagno-

sis to be made? If the physician does approach the relatives, what responsibilities does he or she have for the effect that participation in such testing may have on their lives? As the repertoire of tests grows, these questions will need to be addressed by every physician.

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Tumors of the Urinary Tract

TUMORS OF THE KIDNEY, ureter, and bladder are a source of major morbidity and mortality in the United States. It is estimated that more than 78,000 new cases will be diagnosed in 1992, accounting for 10% and 4% of new cancers in men and women, respectively. More than 20,000 deaths will result from these disorders. These are sobering figures, but cautious optimism is justified for improved therapeutic results in the 1990s. Improvements in diagnostic techniques, clearer understanding of molecular and chromosomal markers of biologic behavior, multimodality therapeutic approaches, and use of biologic therapies give hope for both better quality of life and improved survival.

Some important advances have been made in elucidating the molecular genetics of genitourinary cancers. For example, nonrandom chromosomal abnormalities occur in patients with renal carcinomas and, in selected instances, have led to screening of family members, early detection, and cure. Bilateral renal cancers in young patients and a strong family history should alert the internist and urologist alike to the possibility of an inherited genetic abnormality. Trisomy 7 occurs in a substantial number of urologic tumors, including renal carcinomas. Similarly, von Hippel-Lindau disease may be associated with a high frequency of renal cancers. The gene for von Hippel-Lindau disease has been mapped to an oncogene locus of chromosome 3p25. This chromosomal location may be important in the genesis of other cancers, including small-cell carcinoma and certain ovarian neoplasms.

Bladder cancer, too, is associated with many chromosomal alterations, including trisomy 7, monosomy 9, and alterations in chromosome 5. In selected instances, prognosis has been correlated with specific genetic alterations of the tumor. Indeed, in some centers specific therapies for superficial bladder cancer may be influenced by these "molecular markers."

In this month's issue of the journal, two well-respected and erudite leaders in urologic cancer, Drs See and Williams, review the current status of urinary tumors.[1] They provide a detailed overview of current methods of diagnosis and treatment and highlight areas of active investigation. Two specific topics deserve further comment.

There is a continued interest in a multimodality approach to managing invasive bladder cancer. Once the neoplasm has invaded the lamina propria and involves the muscularis, radical cystectomy has been the traditional treatment of choice. This procedure causes substantial morbidity. It requires an ostomy appliance and quite often results in impotence, due to the commonly performed accompanying prostatectomy. With advances in surgical technique, both of these complications can be minimized.

Creation of continent urinary pouches, using innovative surgical techniques, now obviates the need for complicated external ostomy appliances, and more centers are now using continence-sparing urinary diversions. Likewise, improvements in the anatomic delineation of the nervous and vascular supply to the male genitalia have resulted in surgical techniques (nerve-sparing procedures) that preserve potency.

Systemic chemotherapy of metastatic bladder cancer has also advanced, and slowly improved survival rate and substantial tumor shrinkages in both the primary cancer and metastases have been documented. In some patients these beneficial effects have persisted. The rationale for using chemotherapy for muscle invasive disease, aimed at "down staging" the tumor, is to preserve the bladder while eliminating any accompanying micrometastatic disease. Multimodality therapy consisting of "up-front" chemotherapy followed by radiation therapy delivered to the primary organ may prove to be a reasonable alternative to radical cystectomy in some patients, but further studies are required.

Renal cell carcinoma, sometimes dubbed "the internist's tumor," is nicely reviewed by See and Williams. Early diagnosis greatly increases curability in this disease. Patients who are fortunate enough to have an incidental mass found during an evaluation for nonkidney-related problems generally have a more favorable prognosis when compared with those first diagnosed with paraneoplastic syndromes or symptoms related to metastases. Unfortunately, the therapy for advanced forms of renal cell cancer has not greatly improved. Biologic response modifiers, such as interleukin-2, interferon, and tumor necrosis factor, have proliferated, but most patients do not benefit greatly from use of these agents. As we begin to understand the biology of renal cell cancer better, we should begin to apply to larger patient populations the few therapies that are effective in selected patients.

In the next decade, many diverse biologic preparations will be available for treating human cancer. The use of single agents has generally been disappointing so far. Now, however, we are beginning to appreciate and to understand the multiple actions of biologic therapies and are finally able to evaluate such therapies in the clinic. We have powerful tools to diagnose and stage renal cell cancer, as reviewed so nicely in this issue of the journal. The next few years should bring correspondingly effective therapies for treating renal cancer that has spread beyond the confines of the kidney.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Health Problems in the Chinese in North America

To the Editor: There are about 780,000 persons of Chinese lineage living in the ten states for which this publication is the official medical journal. Most are from the southern Chinese province of Guangdung. Its capital is Guangzhou, formerly Canton; hence, the name Cantonese has been used broadly to include all those from this province. A sizable number of ethnic Chinese have come by way of familial sojourns in various Southeast Asian nations such as Vietnam. More recent immigrants have come from Hong Kong, Taiwan, and now all parts of China. Of the 1.65 million Chinese Americans in the United States, most are American-born.

As the population of persons of Chinese descent continues its dramatic growth in the western United States, these few observations on their health predispositions may prove useful.

One of the major hematologic problems is the thalassemia syndromes. Obvious hemolysis is less of a problem than microcytic, hypochromic Wintrobe indices, either with or without mild anemia. Iron content may need to be evaluated, and genetic counseling may be appropriate. Hyperthyroidism is common, and muscle weakness is more frequent than in the general population.[1] Intestinal lactase deficiency is so ordinary that many patients learn to drink milk to avoid constipation. Colon cancer is the most frequent malignant neoplasm at Chinese Hospital.[2] While nasopharyngeal carcinoma is of lower prevalence, it strikes Chinese men more often than it does most other ethnic groups.[3] Its effect was sufficient to convince the venerable Dr Francis Sooy once to recommend empiric biopsy in any young Chinese man with nasopharyngeal symptoms slow to resolve. Distracting pruritus occurs early in life among southern Chinese due to cutaneous senescence that is premature compared with other ethnic groups. It is manifested early as dry skin (xerodermatosis) and crosses over into psoriasis and atopic dermatitis. The eyeball is longer in the anteroposterior axis, which frequently causes myopia and retinal detachment.

Although hepatitis B and tuberculosis are not unique to the Chinese population, the high incidence of these infections must always be kept in mind when dealing with these patients. It was apparently hepatitis B that led to the high incidence of hepatocellular carcinoma among the Chinese, just as the rarity of placental carcinomas among Asian women in the United States, contrasting with its high incidence in parts of the Far East, also suggests environmental factors.[4]

Of important therapeutic implication is the relatively faster acetylation rate seen among Chinese compared with other racial groups for drugs such as procainamide, isoniazide, and hydralazine. Lupus reactions seem to be uncommon, thus removing this potentially toxic limitation on the use of these agents.

Curiously, despite the old clinical saw that all cases of Huntington's chorea in the United States can be traced to one family, there is living in San Francisco a family from Guangdung with this neurologic disorder.

Hypertension is common with all its usual complications but is far less serious than in African Americans. Diabetes mellitus appears to be less frequent in the Chinese than in the rest of the American population.[5] Coronary artery disease is shifting its façade from ischemic cardiomyopathy among elderly Chinese to angina pectoris or myocardial infarction syndromes in the younger population. In Shanghai, serial studies have shown a progressive rise in mean serum cholesterol levels as that populace has become more westernized.

Certain customs may confuse American clinicians. Chinese girls from some districts of Guangdung use their fingers to pinch lower paratracheal subcutaneous fat to fill out the space between the trachea and the sternocleidomastoids bilaterally. Over the years, this practice creates a "pseudogoiter" that may nonetheless be hiding genuine thyromegaly. For sickness, moxibustion, a practice of burning herbal leaves on the skin, might be used. For pain, hard metallic objects such as tablespoons might be employed to forcibly scrape the skin to draw off noxious substances. These practices leave behind burns or ecchymoses that immediately conjure up visions of bizarre disease or elder abuse in the minds of unwary clinicians.

These are examples of observations that vary in scientific foundation. Better substantiation is needed, but interest and funding are inadequate. Research into diseases of high incidence provides larger pools of scientific data; research into diseases of low incidence may clarify pathogenicity when comparative population studies are done. Further research into these health predispositions in the Chinese-American population would thus be of distinct benefit to the general population whether the focus is on a disease of high or of low incidence.

To help give direction in addressing these ethnic issues, the Chinese Hospital medical staff began a biennial conference on health problems related to the Chinese in North America. In 1992 it will be held at the Sheraton Palace Hotel in San Francisco between June 18 and 21. Topics covered include medical science, nursing, optometry, health care delivery, and traditional Chinese medicine. Inquiries should be directed to the Medical Staff Office, Chinese Hospital, 845 Jackson St, San Francisco, CA 94133-4899, (415) 677-2480.

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More On the 'Gag Rule'

To THE EDITOR: I hesitated to respond to Dr Laura Hammons's letter in the December 1991 issue[1] because so much has been written about the abortion issue with so little effect. Her letter was so irrational and misguided, however, that I finally had to respond.

Her contention is that the "gag rule" prohibiting physicians from discussion of abortion is only a monetary issue. Medi-Cal (California's medicaid program) pays $206 for an abortion. In contrast, prenatal care is reimbursed at $961, and, for a normal delivery, newborn care is $566. If the infant has drug withdrawal, is infected with the human immunodeficiency virus, or is premature, the cost of care is $4,509. The welfare payment for one person is $326 per month and for a family of two is $535. In addition, the mother will probably get supplemental food vouchers, and the child will receive Medi-Cal coverage for ongoing medical expenses. Every birth costs the taxpayers many times the cost of an abortion, so if the question of morality is not important, Dr Hammons should be an abortion advocate.

She objects to her taxes going to support abortions, referral for abortion, or abortion counseling for poor women who voluntarily request them, but we all have objections to some of the things our taxes pay for, such as military equipment that does not work, tobacco subsidies, and photo-opportunity-rich, policy-poor political junkets.

The issue is a matter of free speech. When speech is restricted by application of a penalty based on the content of the speech, it is not free. This particular speech is part and parcel of medical practice. It is not political speech or opposition to or advocacy for some governmental policy. Physicians are not prohibited from the latter, only from discussing medical options, one on one, with their patients. Drs Sugarman and Powers have provided an excellent analysis of the constitutional issues involved.[2]

Obviously, if our only concern were rational, secular, good public policy, we should all be promoting family planning and abortion to control the population that is outstripping our resources. This leads me to believe that the opponents of free speech, good medical practice, and safe abortions have a different rationale, namely, a set of moral values that they want to impose by governmental power on all of us.

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Treating Status Epilepticus

To THE EDITOR: In the otherwise excellent review of status epilepticus by Dr Watson,[1] the management outline presented does not follow traditional or practical resuscitation protocols. First, the initial management should consist of securing the ABCs (airway, breathing, circulation), which includes ensuring that the airway is patent and that adequate air exchange is occurring. Nothing, including oral airways, should be forced into the mouth. Although flexible nasal trumpets may be helpful, their use should be balanced by the risk of increasing intracranial pressure, and they are contraindicated in patients with facial trauma. Endotracheal intubation is frequently necessary. Because the teeth are often clenched and nasotracheal intubation is relatively contraindicated because of the possibility of increases in intracranial pressure, orotracheal intubation should be done after "crash" anesthetic induction with thiopental sodium and the short-acting paralytic agent succinylcholine chloride if there is no contraindication. An added advantage to thiopental is that it may stop the seizures for a short time by itself and often is sufficient to loosen the clenched teeth without using paralytic agents. During this period special attention to cervical spine control is paramount because trauma, either before or after onset of the seizure activity, may have caused injury to the cervical spine.

While the airway is being secured, rapid intravenous (IV) access should also be obtained. Rather than routinely giving 25 grams of glucose, though, it seems pertinent to measure fingerstick blood glucose from blood drawn at the time of the IV insertion. This takes approximately a minute. I agree that 100 mg of thiamine hydrochloride should be given, but it does not have to precede glucose administration as implied. Therapy for documented hypoglycemia always takes precedence over the theoretical risk of producing Wernicke's encephalopathy—which is not likely to occur over minutes anyway.

Finally, how does administering 20 mg per kg of phenytoin sodium in an average-sized adult (60 to 80 kg) at 25 mg per minute equate to 20 to 40 minutes? By my arithmetic, it should take between 48 and 64 minutes. Since 60 minutes appears to be the critical outside limit for the duration of tonic-clonic status epilepticus, and it usually takes more than a few minutes to get to the hospital, secure the ABCs, mix medications, administer lorazepam, and so forth, why not go directly to the faster-acting barbiturates if benzodiazepines fail? As long as someone who can manage an airway is present, it seems impractical and perhaps dangerous not to stop the seizures as quickly as possible. Phenytoin, which has not been shown to be very efficacious in status epilepticus or seizures due to any cause other than idiopathic epilepsy, can then be given after or coincidentally with phenobarbital if desired.

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* * *

Dr Watson Responds

To THE EDITOR: I appreciate Dr Wrenn's comments and interest in my review article on status epilepticus.[1] I have no quarrel whatsoever with his comments concerning the initial evaluation and management of the patient presenting to the

emergency department in status epilepticus. I mentioned that the initial treatment of patients in status epilepticus begins with an assessment of cardiorespiratory compromise and function, but I did not detail the actions involved because these are standard procedures undertaken by emergency department physicians and their teams. I thank Dr Wrenn for presenting the details of this initial action. Also, I have no quarrel with measuring fingerstick blood glucose before administering glucose, and I agree that thiamine hydrochloride should be given either before, simultaneous with, or just after glucose is administered. I personally have seen a few cases of Wernicke's encephalopathy produced by administering glucose alone.

I would take exception to the comments concerning the lack of efficacy of phenytoin sodium in treating status epilepticus or seizures due to any cause other than idiopathic epilepsy. Several studies have shown phenytoin to be quite effective in the acute treatment of status epilepticus.[2-6] Phenytoin is also used to treat a variety of partial and generalized seizure types that do not fall under the heading of idiopathic epilepsy, such as simple partial seizures, complex partial seizures, and secondarily generalized tonic-clonic seizures. Of course, the main disadvantage of phenytoin in treating status epilepticus is the time required to give an average loading dose at a rate that does not cause hypotension or cardiac arrhythmia. This problem is usually obviated by administering lorazepam, which often terminates status epilepticus for as long as 12 to 24 hours, allowing ample time to infuse phenytoin.

The problem of combining a benzodiazepine, which has often been administered in the field by paramedics, with phenobarbital was discussed in the article. This combination may cause abrupt respiratory arrest and hypotension, which just add to potential morbidity in this setting.[7-14] As the results of the multicenter prospective Veteran's Affairs study[15] become available, we will have better information with which to make some of these difficult therapeutic judgments.

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Lessons From the Practice

Fear of Needles

STEPHEN FISK, MD, PhD, *Santa Clara, California*

The month of October 1989 was a time of major dislocation for the San Francisco Bay Area. For me, the important day was not the 17th—earthquake day—but the 26th. This was the day I encountered Sean Orkin's* blood.

"Oh, shit!" doesn't even begin to describe how I felt when I stabbed myself with a needle while sewing his chest tube in. Sean was dying of the acquired immunodeficiency syndrome (AIDS). I had just saved him from a premature death by decompressing his tension pneumothorax. As a result, he would have two additional days of life on a ventilator. I, on the other hand, was off to the needle-stick wars.

In the time-honored fashion of all members of my family who face a devastating crisis, I immediately set out on the path of denial. I finished my interrupted stitching and then walked to the sink and spent the next five minutes milking a third of my blood volume out the hole in my finger while swearing to myself. The rest of the intensive care unit was busy helping Sean, wailing at my uncertain fate, and calling the infection control nurse for advice in filling out the inevitable "incident report" that would be stored in the bowels of the hospital for eternity.

When Paula, the infection control nurse came in, she gave me a 45-minute time limit, something that I had not known about until that very moment. "I'm calling Mark right now," she said. "You have to make 'the AZT decision' within the next 45 minutes."

Mark arrived within 15 minutes with a copy of the "latest" advice from the Centers for Disease Control on my options. Mark is a great one to have around. He is one of the brightest people I've met in the infectious disease field. He also is the only person I know who can tell a joke with the enthusiasm of a mortician. When the situation is more serious, as I was quickly surmising that mine was, he becomes completely funereal. From the expression on his face, I knew that I was already dead, despite the quoted odds (1 in 250) of my becoming positive for the human immunodeficiency virus (HIV). In addition, I now had less than half an hour to swallow 200 mg of zidovudine to inhibit those little retroviruses from starting their slow march through my lymphocytes.

"Incidentally," he deadpanned, "these are the possible side effects of taking this stuff for a month: nausea, anorexia, and fatigue. Insomnia—maybe even leukemia in 15 years or so." With that as a send-off, I took off at a dead run for the pharmacy. Fifty-one minutes after the puncture, I gobbled the first of 120 doses of zidovudine. I had a really great month to look forward to. The blood tests were next.

Paula, the infection control nurse to the rescue! As she casually stuck a needle in my arm, we discussed the astronomical number of tests that she or someone else would do in the next year: complete blood count (zidovudine can wreck your marrow), liver function (zidovudine can whip your liver), HIV tests at six weeks, three months, six months, and one year. If you think I was nervous before, you need to know that I was the kid who at age 8 required five nurses and attendants to restrain him while the pediatrician immunized him.

After this, I got to go to lunch. Boy, was I hungry. That was the last time for a month. I'm a great lover of food. I look forward to meals and goodies. For one solid month while on the zidovudine, I couldn't have cared less. That was only the beginning. Taken alone, none of the side effects were especially bad. Taken in aggregate, however, they had a synergistic effect. I felt crummy. Do you know how hard it is to activate your denial system when you are constantly reminded of your "infirmity"? Even I, an accomplished denier, was hard-pressed to participate in my favorite defense mechanism.

Next, there were all the questions about the future. For openers, did I even have one? Blood donation, yea or nay? If not now, when? Whom do I tell? When?

Finally, there was the real psychological issue of vulnerability. I was 48 years old at the time. I have a negative family history for just about everything. Most of my forebears lived into their 80s and 90s. I was in great health just before the needle stick. All of a sudden, I had to face the possibility of my death—and not a particularly pleasant one, either. I had only to walk back into the ICU and look into Sean's room to see my possible future. Sure, the odds said "no." Sean said "yes" by his presence. After he died, he said "yes" by his absence. Within about a week, denial and repression had accomplished their usual magic. Except for feeling lousy, I was back to mildly abnormal—maybe.

The occasional, possibly exercise-related chest pains that I'd been experiencing now assumed a new importance. Maybe I ought to get an electrocardiogram despite never having had one before. Surprise, the results were abnormal, supine and at rest. Was this the time I needed to see that? Next a treadmill. Equivocal at 15+ mets. Next, a thallium treadmill. Normal. Whew!! Two thousand dollars worth of psychosomatic workup in a supposedly rational, nonsomatizing person. A doctor! Once again proved vulnerable.

Through all this there was the famous "test-waiting" phenomenon. They all take time. The results get lost. If they don't get lost, the identifying numbers get lost. Remember, AIDS tests don't have names attached in California. We have created a system that ensures privacy for the individual while

*The patient's name has been changed.

(Fisk S: Fear of needles. West J Med 1992 May; 156:560-561)

From the Department of Anesthesiology and Intensive Care Medicine, Kaiser Foundation Hospital, Santa Clara, California.
Reprint requests to Stephen Fisk, MD, Department of Anesthesiology and Intensive Care Medicine, Kaiser Foundation Hospital, 900 Kiely Blvd, Santa Clara, CA 95051.

at the same time dehumanizing the person. Hey, I'm Steve Fisk, not EL-948-67.

The final issue that came up during the months of testing was the result of the geographic area in which I live. No Bay Area newspaper can be read on any given day without three articles on AIDS appearing in the first five pages. I became sensitized to those four letters. I still am. My gracious employer picked that particular time to send out a form that I had better sign, by God. It stated that they had done everything in their power to inform me of all the needle-stick hazards of my job and simultaneously absolved them of all guilt in the event of a repeat of my stupidity. I certainly didn't need this communication from the litigation-fearful. Nonetheless, I got it.

It's been two years now, and I'm still HIV-negative. The questions that were at once the easiest and hardest to answer were the ones I was asked most often by relatives and close friends. "Would you do it again? Will you take care of HIV-positive patients in the same way again? Will you take care of them at all? Will you expose yourself to that kind of risk again? Will you be more careful next time, if there is a next time?"

The answers are all the same: "Yes." I learned a great deal about myself by making a potentially fatal mistake. Who I am, or at least who I think I am, would be different if I couldn't answer "yes" to all those questions. But the answers are mine only. They will not be the same for all of us, nor do they have to be. What is important is that we ask the questions, that we learn from the answers, and that we cease to be deluded by the illusion of our own invulnerability.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

TO A CASTING DIRECTOR DEAD FROM AIDS

You cast me in my first play
after weeks of climbing the stacks of photos
using your own mallet like some Egyptian building a tomb.
To open a resume, you knew, was to open a vein.

We drank coffee from a Deli on 46th Street
and you would start to cough
already your lungs no longer caring
already some enemy singing.

Once we climbed the dark stairs of a 2nd Avenue Theatre
neither of us brave enough to take the elevator.
Filing and loving actors
is enough handicaps.

Why did it take me so long to know
the part you picked for yourself was born with broken arms?

For months, years, you defined courage and carried it inside you;
that was the real solo
a dolphin in your lungs wanting to surface, to sit up for the sun.

Now memory forges a horseshoe around my heart.
So there it is, one more play over
the seats folded up for the last time in prayer.

LAVONNE MUELLER©
Iowa City, Iowa

Poems

HISTORY

Begin with innocence. Then, the missing
bones. When did it happen? Who knows

how loss occurs? No photographs. No
memory. This is what I have

to go on: the hospital report,
my father's words. In front of me:

my feet, each the size of his finger.
Now, the gnarled roots of trees.

For thirty years, this question: how
do you mourn for something you never had?

INCUBATOR

As if from a goldfish bowl, through
small, fogged eyes. And nowhere

do I find you, even though I know
you must have been there. The hands

that turn me are the nurse's hands;
the eyes watching are my father's.

But where is the body from which I was
born unwhole? Your body almost

died giving birth to mine. Mother,
after all these years I am asking why

you never told me. We touch through
a sheet of glass. Give me your hand—

help me find those missing bones, clear
that infant's eyes. Open them—wider.

X-RAY

I am eight months old and looking
for you, daddy, at the other

end of the metal table. Your eyes
told me all I need to know—

if I could just remember. I watch
the large machine rattle down its track,

feel the cold on my skin,
when all these years I wanted

the memory of your hands holding my
twisted feet in the right position.

Remembering this now I am
still that eight month old,

your son, staring into the eyes
of that machine, trying to find you

in the reflection it gives back
—nothing from the waist down.

BODY LANGUAGE

What is a scar if not the memory of a once open wound?
You press your finger between my toes, slide

the soap up the side of my leg, until you reach
the scar with the two holes, where the pins were

inserted twenty years ago. Leaning back, I
remember how I pulled the pin from my leg, how

in a waist-high cast, I dragged myself
from my room to show my parents what I had done.

Your hand on my scar brings me back to the tub
and I want to ask you: What do you feel

when you touch me there? I want you to ask me:
What am I feeling now? But we do not speak.

You drop the soap in the water and I continue
washing, alone. Do you know my father would

bathe my feet, as you do, as if it was the most
natural thing. But up to now, I have allowed

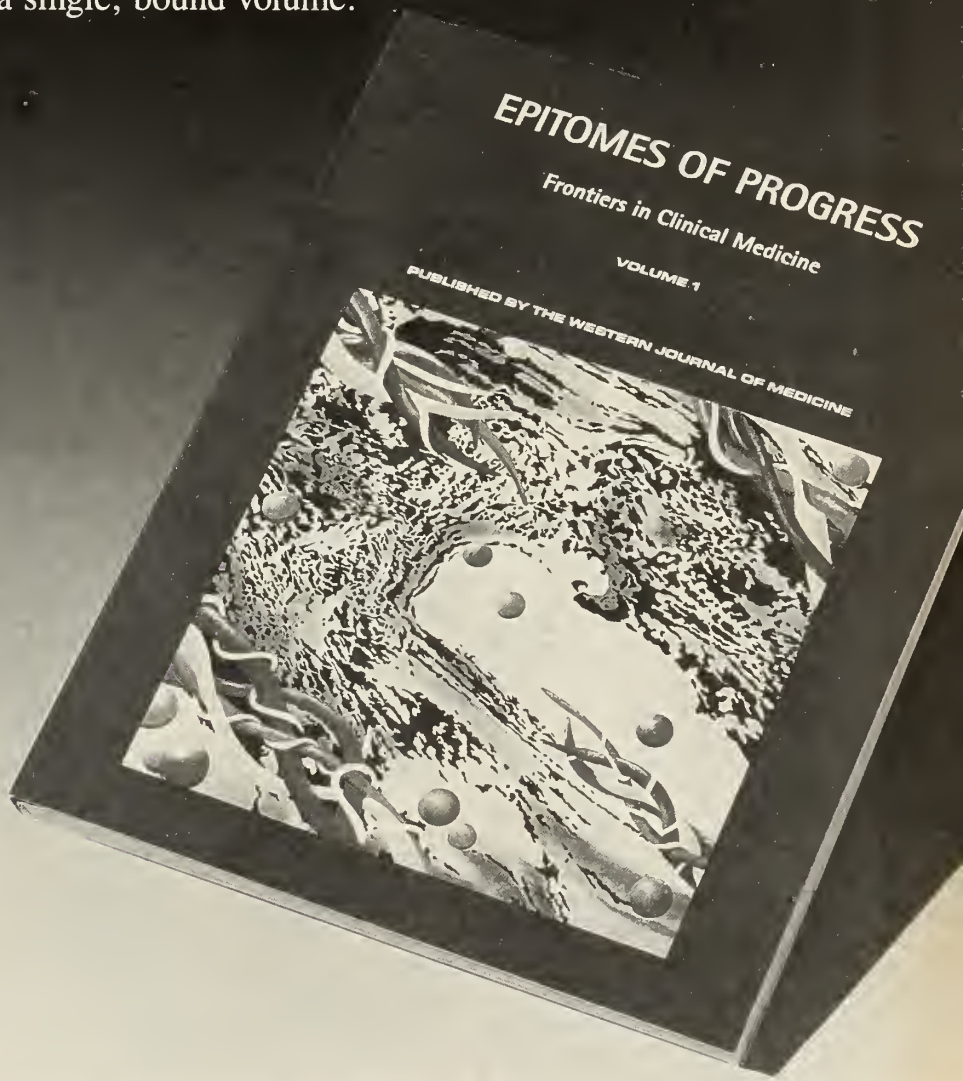
only two pair of hands to touch me there,
to be the salve for what still feels like an open wound.

The skin has healed but the scars grow deeper—
When you touch them what do they tell you about my life?

KENNY FRIES©
Provincetown, Massachusetts

epitome

i-'pit-ə-mē\ *n* [L, fr. Gk *epitomē*, fr. *epitemnein* to cut short, fr. *epi-* + *temnein* to cut — more at TOME] (1520) **1 a** : a summary of a written work **b** : a brief presentation or statement of something **2** : a typical or ideal example: EMBODIMENT (the British monarchy itself is the ~ of tradition — Richard Joseph) **3** : Plural — *Epit-o-mes* — A regular FEATURE of *The Western Journal of Medicine*, now available in a single, bound volume.



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Books

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5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983
7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

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112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 105,000; a growing area with new businesses and a stable economy. A 30% plus growth in population and jobs is predicted for our area during 1990s.

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Contact:
Tulare District Hospital
Physician Recruiting Office
PO Box 90112
Los Angeles, CA 90009
(800) 468-2687

PRIMARY CARE PHYSICIAN, OSTEOPATHS, AND PHYSICIAN ASSISTANTS wanted for expanding eastern Washington clinic. Full- and part-time positions available. Located in prime recreational area. Skiing, sailing, fishing, hunting all within a short distance. Enjoy mild climate, excellent schools and a major university branch campus in growing community of 100,000 plus. Challenging work in a superbly equipped clinic with state-of-the-art lab, x-ray, laser, and endoscopy. Above average compensation and benefits including malpractice, health insurance, and CME. Contact Dr Stephen L. Smith, 310 Torbett, Richland, WA 99352; (509) 545-8340 or FAX (509) 946-7666.

INTERNAL MEDICINE—WASHINGTON. Prominent 100 physician multispecialty clinic in Pacific northwest is seeking a BE/BC General Internist for summer/fall 1992. Guaranteed salary and partnership track available. Excellent benefit package. Abundant four-season recreational opportunities in family-oriented community. Send CV to Peter Rutherford, MD, PO Box 489, Wenatchee, WA 98807.

FULL-TIME, non-tenured track position to work as an attending physician in the Division of Emergency Medicine, Department of Surgery at the University of Utah School of Medicine/teaching hospital. Must be residency trained or BC in Emergency Medicine. Reply to MS Linscott, Jr, MD, 50 N Medical Dr, Salt Lake City, UT 84132; (801) 581-2730. Position will be open June 15, or until suitable candidate is identified. The University of Utah is an Affirmative Action/Equal Opportunity Employer.

SOUTHERN CALIFORNIA. Family Practice physician position available in Riverside County. Guaranteed income, excellent benefits with early partnership. Send résumé to Number 265, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 566)

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PHYSICIANS WANTED

CUPERTINO MEDICAL CENTER

NORTHERN CALIFORNIA

We are seeking motivated Primary Care physicians to join our growing Urgent/Primary Care clinic. BC/BE physicians in the field of Internal Medicine, Family Practice, or Occupational Medicine are invited to apply.

The Cupertino Medical Center is located in the heart of Silicon Valley and is a leader in the provision of Urgent Care and Primary Care services. You will lead a team of health care professionals, work in a pleasant, modern environment, and enjoy the opportunity provided by our established base of loyal patients.

Ability to perform treadmill testing and sigmoidoscopy is desirable.

This unique opportunity offers very competitive compensation and benefits, flexible work hours, and early opportunity of partnership. Equally important is the chance to locate to this growing area, which abounds in cultural and recreational activities.

Direct inquiries to Mark Congress, MD, Medical Director
20289 Stevens Creek Blvd, Cupertino, CA 95014, (408) 996-8656

GERIATRICIAN. Position available for an Assistant/Associate Clinical Professor in the Department of Medicine/Division of General Internal Medicine/Geriatrics at the University of California, San Diego. Must be BC Internist or Family Physician with training and experience in Geriatric Medicine. Position is 80% clinical to provide primary and specialty care to seniors enrolled in managed care programs and 20% teaching. Preference will be given to candidates with fellowship training and/or have Certificate of Added Qualifications in Geriatrics. California license or eligible to apply required. Salary and benefits are very competitive. Salary related to rank and step of appointment and based on UCSD salary scales. Reply by May 29, 1992 to Joe Ramsdell, MD, UCSD Medical Center, Department of Medicine (8415), 225 Dickinson St, San Diego, CA 92103-8415; (619) 543-6275. AA/EOE.

SAN FRANCISCO BAY AREA. Outstanding opportunity for young Dr Welby to take over an established and very successful Family Practice. Loyal patient base and experienced two person office staff welcome new physician to this home office practice. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411, or FAX (415) 399-0411.

THE MEDICAL CENTER AT PRESCOTT, ARIZONA is recruiting for a Physician, BC/BE, in Internal Medicine, Family Practice, or Geriatrics. The Medical Center is comprised of a 217-bed General Medical and Surgical Facility with a 60-bed Nursing Home Care Unit and a 208-bed Domiciliary. Salary negotiable. Send CV to Rita Heidisch, MD, Acting Chief of Staff, VA Medical Center, Prescott, AZ 86313, or call (602) 776-6009. An equal opportunity employer.

INTERNAL MEDICINE—Southern California. Challenging career opportunities for specialists in Internal Medicine desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

CARDIOLOGY, HEMATOLOGY/ONCOLOGY, GENERAL INTERNISTS. Private practice opportunities available in the states of Washington, Nevada, Texas, Florida, and Louisiana. For details, please call Eloise Gusman; (800) 535-7698, or send CV to PO Box 101656, Fort Worth, TX 76185.

FAMILY PRACTICE. Join an established group of five Family Practitioners in the Sparks/Reno, Nevada area. Excellent practice situation. For details, call Eloise Gusman; (800) 535-7698, or send CV to PO Box 101656, Fort Worth, TX 76185.

CARDIOLOGIST, full-time BC/BE, invasive/non-invasive, inpatient/outpatient for practice at general hospital in association with two Cardiologists and five Internists leading to partnership. Excellent vacation schedule and competitive salary. Twenty-five minutes from San Francisco. Reply to San Mateo County Hospital, Attn: Mark Highman, MD, 222 W 39th Ave, San Mateo, CA 94403; (415) 573-3786.

EMERGENCY PHYSICIANS. Imagine practicing in a cozy location near the splendor of world famous Lake Tahoe! Churchill Community Hospital is looking for Emergency Director and Emergency Staff Physician. $116-150K. Malpractice and overhead paid. Primary specialty BC/BE, ATLS, ACLS. Call (702) 423-3151/Jeffrey Feike, Administrator.

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The University of Utah School of Medicine, Division of General Medicine is offering full-time positions for BC/BE Internists at the Instructor, Assistant Professor, Associate Professor levels. Rank and salary commensurate with qualifications. Opportunities include patient care, teaching of medical students and residents, administration, and clinical research. Applications must be postmarked by May 31, 1992; applications submitted after the deadline may be considered if no qualified candidates have applied by that deadline. An equal opportunity employer. Contact John H. Holbrook, MD, Department of Internal Medicine, University Hospital 4B-120, Salt Lake City, UT 84132.

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(509) 482-2164
FAX: (509) 482-2187

(Continued on Page 567)

(Continued from Page 566)

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Internist wanted for beautiful Salt Lake City area. Excellent skiing, camping, fishing and hunting. Looking for aggressive, hard-working Family Practitioner to expand clinic. Complete laboratory facilities and x-ray in ambulatory care type setting. Call or write: **Robert Davis, MD, Director, Family Medical Center, 1519 W. 9000 South, West Jordan, UT 84088; (801) 562-9100.**

BC/BE RADIOLOGIST. Exceptional northern California location. General diagnostic radiology, including invasive. All imaging modalities represented. Academic appointment available. Join three BC Radiologists. Contact Carol Westfall, Cejka & Co, 222 S Central Ave, Ste 700, St Louis, MO 63105; phone (800) 765-3055, FAX (314) 726-3009.

IMMEDIATE OPPORTUNITY for BC/BE Primary Care physician in expanding "group without walls" in Glendale, California, twenty minutes north of downtown Los Angeles. Salary plus incentive plus benefits. No buy-in necessary. Contact Director, Physician Services, Glendale Memorial Hospital, (818) 502-2371.

100 MEMBER multispecialty group seeks BC/BE Family Practitioners, Pediatricians, General Internists, Otolaryngologist, and Dermatologist in pleasant, growing northern California community two hours from San Francisco, Yosemite, and the Sierras. Excellent benefits, salary and facilities. Send CV to C. V. Allen, MD, Medical Director, 600 Coffee Rd, Modesto, CA 95355.

NATIONWIDE TRAVEL. Health research organization seeks physician for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individual will be part of a large medical team conducting health examinations in government mobile exam centers traveling to 88 areas of the US through 1993. Must be licensed in one state. One year minimum commitment and full-time continuous travel required. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline, (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD, EOE/M/F/V/H.

THE UNIVERSITY OF CALIFORNIA, San Francisco and the Central California Faculty Medical Group seek a staff Cardiologist to join the teaching faculty at their affiliate, Valley Medical Center of Fresno. Applicants should be BC/BE. Full invasive and non-invasive cardiology services are available. In addition to the academic participation, there is potential for private practice experience. Geographic location offers a large population with a variety of cardiological disease. VMC has 350 active beds and conducts residency training programs in most major clinical disciplines as well as a fully accredited cardiology fellowship. The central California location offers enjoyable and affordable California living. Competitive salary and benefits. UCSF is an equal opportunity employer. Address inquiries to Lauren Grayson, MD, Chief of Cardiology, CCFMG, 4910 E Clinton, #101, Fresno, CA 93727.

SOUTHERN CALIFORNIA. Family Practitioner BC/BE or General Practitioner. Multispecialty group in Orange County. Excellent compensation. Call (714) 633-4225.

UROLOGISTS—BC/BE needed for multispecialty group practice in central California and single-specialty group in Tucson, Arizona. Excellent compensation packages and partnership opportunity. All inquiries confidential. Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

SOUTHERN CALIFORNIA. Opportunity for part-time Emergency/Family Practice physicians at urgent care/industrial center in Orange. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

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The Western Journal of Medicine

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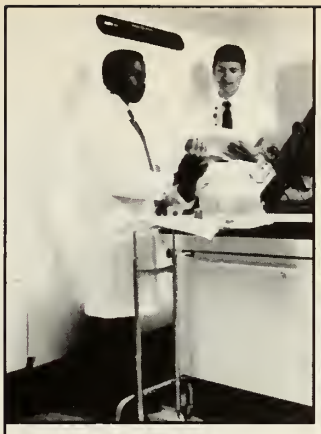

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ARIZONA
Phoenix & Tucson

Anesthesiologists
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Arizona: CIGNA Healthplan, Professional Staffing, P.O. Box 16145, Dept. 49, Phoenix, AZ 85011-6145, (800) 252-2471.

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(Continued from Page 567)

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Overland Park, KS 66211
1-800-533-0525

BC/BE FEMALE INTERNIST sought to join established female Internist in a southern California private practice. Send CV to Number 261, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

TWO FULL-TIME MD POSITIONS AT THE LEVEL OF ASSISTANT/ASSOCIATE PROFESSOR OF FAMILY PRACTICE available in the Family Practice Department, University of California, Davis. Must be BC by the American Board of Family Practice with interest, training, and/or experience in research, academic publication, administration, teaching, and obstetric activities. The positions will remain open until June 30, 1992. Send CV with list of four references to Klea Bertakis, MD, Department of Family Practice, UC Davis, 2221 Stockton Blvd, Sacramento, CA 95817. The University of California is an affirmative action, equal opportunity employer.

GASTROENTEROLOGY—SAN DIEGO. Excellent opportunity to expand present practice or start new one. Confidentiality respected. Collections $350,000. Excellent profits. Greater than 50% private patients. Call Marc Miller; (310) 430-3430.

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SEATTLE. As the result of population growth and reputation, this 28 physician group practice is in need of several recently trained Family Practitioners. This suburban community is situated within minutes of downtown Seattle and within one hour of Mt. Rainier. Remuneration package includes base salary plus incentive and full benefits with partnership after two years. Call rotation every 7th night and weekend. Congenial atmosphere. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

FAMILY PRACTICE—NORTHERN CALIFORNIA BC/BE. Immediate opportunity for an associate. All negotiable proposals considered. Advance to partnership in very lucrative and exciting practice located 30 miles east of San Francisco next to 300-bed hospital. Send CV to Fred Von Stieff, MD, Mount Diablo Hospital, 2540 East St, Concord, CA 94520; (510) 680-8933.

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The deadline for submitting classifieds for the July issue of WJM is May 26. Send your advertisement to:

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CALIFORNIA, BERKELEY. Experienced Emergency Room, Family Practice, Internal Medicine, and Urgent Care Physicians sought to staff an inpatient service at a large community hospital. Excellent hours (no nights) and compensation. Applicants must be BC/BE in either Emergency Medicine, Family Practice, or Internal Medicine. Job parameters may be configured to accommodate full- or half-time commitments. Please send CV to Joan Wendell, Office Manager, PO Box 5138, Berkeley, CA 94705.

PRACTICE IN SAN DIEGO. BE/BC Family Practitioner or Internist needed for busy private practice opportunity leading to partnership. Competitive salary and compensation package. Beautiful San Diego lifestyle. Send CV to Joseph Browne, MD, 1809 National Ave, San Diego, CA 92113; or call (619) 234-8171, ext 311.

FAMILY PRACTITIONER FACULTY/DIRECTOR OF GERIATRICS needed at community USC/LLU affiliated residency in suburb 15 minutes from downtown Los Angeles, mountains, and Pasadena. Excellent salary and benefits. Send CV to Jack Yu, MD, 801 S. Chevy Chase Dr, #201, Glendale, CA 91205; (818) 500-5594.

EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

MONTEREY. MULTIDISCIPLINARY, four physician clinic. Immediate need for Family Practitioner. Progressive modern clinic: Industrial, private, and personal injury. Pat Callow, 550 Camino El Estero, Ste 204, Monterey, CA 93940; (408) 375-5151.

GENERAL INTERNIST—BE/BC needed to join me in my successful, rapidly expanding practice in a beautiful new office in southern Marin County. Part-time position available immediately, leading to partnership. Must be US university trained, willing to work hard, ambitious, and desiring a solid future practice. Submit CV to PO Box 880, Larkspur, CA 94977-0880.

(Continued on Page 569)

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(Continued from Page 568)

PHYSICIANS WANTED

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BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled Family Practice physician to join our highly respected Urgent/Primary Care group with two beautiful Santa Cruz clinics. Flexible scheduling and a comprehensive benefit package. Rapid advancement to full partnership. Please send CV to Stuart Simon, MD, 6800 Soquel Dr, Aptos, CA 95003 and call (408) 662-3611.

NORTHERN CALIFORNIA RECREATION AREA. Multispecialty group has immediate opening for an Internal Medicine practitioner with a particular interest in Critical Care. Clinical activities involve full range of Internal Medicine outpatient and inpatient practice. Beautiful northern California location offers abundant recreational opportunities as well as small town living. Competitive salary and comprehensive benefit package. Please send CV to PO Box 8247, Truckee, CA 96162.

SOUTHERN CALIFORNIA. FAMILY PRACTICE, BC, energetic individual for a rapidly growing three physician practice. Will need to do clinic, hospital, and long term care facilities. Excellent compensation, rapid progression to partnership. Location is 10 minutes from the ocean in a fast growing area near Oceanside. Here is a chance to practice private medicine without bureaucratic problems. Call (619) 630-2422.

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SAN DIEGO STATE UNIVERSITY
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CENTRAL CALIFORNIA—SEEKING FULL-TIME FAMILY PRACTICE PHYSICIAN. Excellent opportunity for Family Physician to join a very successful growing association of Primary/Family Practice providers in private practice. On site x-ray, pharmacy, and physical therapy. Also seven day week Urgent Care. First year net income potential 150K, second year net income potential 200K. One block from hospital. Close to Sequoia National Park, two hours to Los Angeles or the coast. Immediate opening. Janet Giles, Manager, 590 W. Putnam Ave, Porterville, CA 93257; (209) 781-4100.

OB/GYN OPPORTUNITY AVAILABLE. Prestigious community health center in sunny San Diego seeks BC/BE OB/GYN physician. Combine high quality medicine with rewards of serving a truly needy population. Loan repayment possible, competitive salary and comprehensive package. For additional information, please direct inquiries and confidential CV to Joseph Browne, MD, Medical Director, Logan Heights Family Health Center, 1809 National Ave, San Diego, CA 92113; or call (619) 234-8171, ext 311.

PHYSICIANS WANTED

BC/BE FAMILY PRACTITIONER for satellite clinic of prestigious multispecialty group practice. Join one other Family Practitioner and one Physician's Assistant in small town setting with urban culture 20 minutes away. Generous benefit package. Send CV to Donald Benz, MD or Karen Stanton, The Vancouver Clinic Inc, PS, 700 NE 87th Ave, Vancouver, WA 98664; (206) 254-1240.

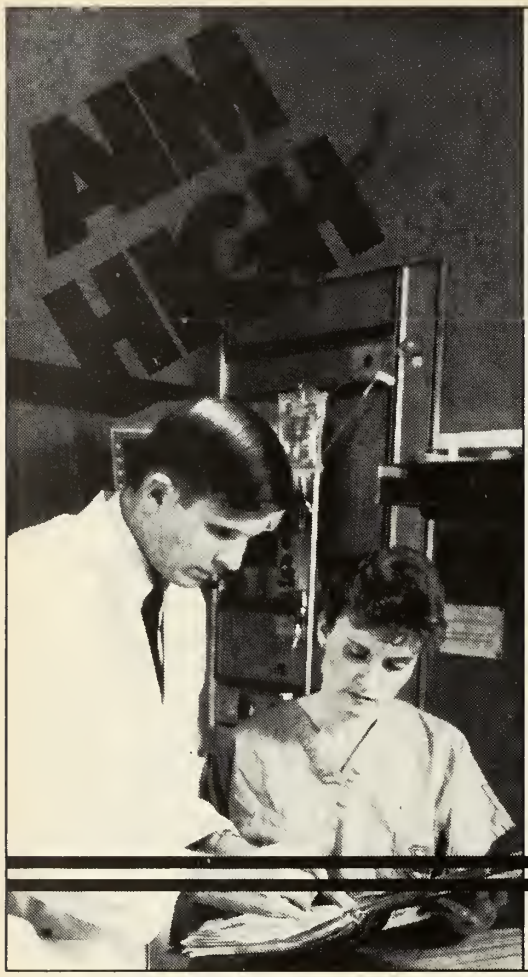
INTERNISTS AND FAMILY PRACTITIONERS. Internists and Family Practitioners needed to fill several positions offered by the Logan Heights Family Health Center. One position involves care of HIV patients. Competitive salary and compensation package. Loan repayment possible. Please send CV to Joseph Browne, MD, Medical Director, LHFHC, 1809 National Ave, San Diego, CA 92113; or call (619) 234-8171, ext 311.

YOSEMITE. Yosemite Medical Clinic is seeking a fourth full-time staff physician experienced in Primary and Emergent Care. ACLS required, ATLS or PALS helpful for occasional emergencies. All outpatient based. Housing provided in Yosemite Valley. Contact Robin Berman; (209) 372-4637, PO Box 547, Yosemite, CA 95389.

CARDIOLOGIST—CALIFORNIA'S SCENIC CENTRAL COAST. BC/BE Non-Invasive or Invasive Cardiologist to join dynamic three person Cardiology practice in beautiful Monterey Bay area. TEE/Nuclear desirable. Unique opportunity. Reply to Unique Cardiac Placements, 1000 S. Main St, Ste 498, Salinas, CA 93901.

EXCELLENT OPPORTUNITY FOR BC/BE INTERNIST to join four Internists in San Jose area with future opportunity to assume practice of retiring physician(s). Exceptional income guarantee and benefit package being offered. Interested candidates call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

(Continued on Page 570)



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(Continued from Page 569)

PHYSICIANS WANTED

ACADEMIC PULMONOLOGIST/INTENSIVIST. Academic Pulmonary/Critical Care physician needed to join a three physician division of Respiratory and Critical Care Medicine at a 400-bed teaching hospital with Stanford University affiliation. The hospital has a full Internal Medicine residency training program and the division is part of a combined three hospital Pulmonary fellowship (SCVMC, Stanford University, and Palo Alto VA). The division's activities include supervision of medical students, residents and fellows, direction of a complete PFT LAB and an eight-bed MICU and participation in clinical research. Address inquiries to Carl M. Kirsch, MD, Division of Respiratory and Critical Care Medicine, Santa Clara Valley Medical Center, 751 S. Bascom Ave, San Jose, CA 95128; or call (408) 299-5514. An equal opportunity and affirmative action employer.

DERMATOLOGIST. Immediate opportunity available for full- or part-time position with University affiliated multispecialty group in one of the most desirable cities. We offer a balanced lifestyle, competitive salary and an excellent benefit package. Send CV to Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

BE/BC FAMILY PRACTITIONER to join one Family Nurse Practitioner, one Pediatric Nurse Practitioner and one OB/GYN Nurse Practitioner, and two part-time OB/GYNs in Walla Walla, Washington. Share call with four practitioners. Competitive salary, excellent benefit package, including vacation up to 32 days per year and professional liability. Public Health Service immediate Loan Repayment slot. Contact Sylvia Arroyo, Clinic Administrator, Family Medical Center, PO Box 515, Walla Walla, WA 99362; (509) 525-6650, or Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant; (509) 865-5898.

PHYSICIANS WANTED

HAWAII. FAMILY PRACTITIONER, INTERNIST, AND PEDIATRICIAN NEEDED for rural underserved area. Full-time position in nonprofit community health clinic. Desire dedicated person to work in multicultural setting. Contact Kathy Garner, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-1458.

FAMILY PRACTICE, BC/BE to join group practice in growing southwestern town. Full service clinic, 280-bed hospital. Offering competitive salary, equal call schedule, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Linda Johnson, 8009 S. 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

NORTHERN CALIFORNIA

San Jose's leading multispecialty group is growing. We are seeking BE/BC physicians in the following specialties:

- Orthopedic Surgery
- Internal Medicine/ General
- Pediatrics
- Urgent Care
- Family Practice
- Occupational Medicine

If you are committed to excellence and strongly motivated for success, we would like to hear from you. Please send your CV to Maureen Forrester, San Jose Medical Group, Inc, 45 S. 17th St, San Jose, CA 95112; **or call (408) 282-7833.** An independent physician group affiliated with Stanford University Medical Center.

PHYSICIANS WANTED

FAMILY PRACTICE RESIDENCY FACULTY POSITION. FULL-TIME ASSOCIATE PROFESSOR. UNIVERSITY OF WYOMING FAMILY PRACTICE RESIDENCY PROGRAM-CASPER. This is an outstanding rural Family Practice Residency Program with 24 residents and nine faculty members. It is affiliated with Wyoming Medical Center, which is currently undergoing a $20,000,000 expansion. Responsibilities include resident supervision in ambulatory and inpatient settings, participation in clinical research projects, direct patient care, and administrative duties. Requirements include BC, a minimum of three years of Family Practice including Obstetrics, and a strong desire to teach rural family medicine. Applicants should include current CV and three references. Competitive salary and benefits. Come join us in beautiful Wyoming. The University of Wyoming is an equal opportunity/affirmative action employer. Final approval will be made by the University of Wyoming. Please contact Jay Swedberg, MD, Acting Program Director, University of Wyoming Residency Program-Casper, 1522 E. A St, Casper, WY 82601; (307) 266-3076.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

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PHYSICIANS WANTED

Western States OPENINGS
Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

ESCAPE those urban hassles and come to scenic northern California. Opportunity available to join two other Internists in private practice. Competitive salary and benefit package available. Contact Mark Oswald of Gielow/Laske Associates, Inc, 306 N Milwaukee St, Milwaukee, WI 53202; (800) 969-7715, FAX (414) 226-4131. Confidential inquiries welcome.

SAN FRANCISCO BAY AREA. Palo Alto Medical Clinic, a 150 physician multispecialty group with a national reputation for innovation and excellence, seeks BC/BE Family Practice physician to join vigorous eleven member department. Exciting opportunity for energetic person to become part of innovative health care team. Competitive salary based on experience. Excellent benefits package. Two year partnership track. Please forward letter of interest and CV to George Perlstein, MD, Medical Director, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

PUGET SOUND. Internist to share equipment, office, and call in high growth community 30 minutes north of Seattle. We seek a fourth physician eager to maintain independent practice and finances, to share expenses and reduce starting costs by first year use of computer, phone, ECG, etc. Buy in later. Ample patient base. Excellent medical community and full service hospitals. Maximal scheduling freedom, but would make own practice management decisions. Well located new office. Contact J. Shaw, MD, 1330 Rockefeller, Ste 210, Everett, WA 98201.

PEDIATRICIAN—SANTA MONICA. Associate needed for rapid takeover of busy, lucrative Pediatric practice. Good coverage weekends. Low overhead. Rare opportunity. Phone Lisa; (310) 829-1752 for details.

CALIFORNIA. The Sacramento Children's Medical Clinic, an ambulatory private practice for children of low income parents, consisting of four offices (one on wheels) needs a BE/BC General Pediatrician. Direct patient care and supervising midlevels for inner city, migrant health and outreach programs. Monday through Friday. Quake-free locale. Spectacular climate. Innumerable recreational opportunities. Competitive salary with equity potential. Contact Gilbert Simon, MD, 1355 Florin Rd, Ste 14, Sacramento, CA 95822, (916) 422-6326.

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PHYSICIANS WANTED

GREAT OPPORTUNITIES IN NORTHERN CALIFORNIA

We're San Jose's leading multispecialty private group practice with nine locations, and seek BC/BE physicians with broadly based high level training to **join our Department of Urgent Care and General Medicine.**

We offer competitive salary, a comprehensive benefits package including retirement and 401K plan contributions, and early access to partnership and stockholder status.

The South Bay area provides a wide range of cultural and recreational activities, good schools, fine dining, and a congenial climate.

If you are committed to excellence and strongly motivated for success, we'd like to hear from you. Send your CV to Maureen Forrester, San Jose Medical Group,* 45 S. 17th St, San Jose, CA 95112; or **call (408) 282-7833.**

*An independent physician group affiliated with Stanford University Medical Center

BC/BE FAMILY PHYSICIAN to join three other Family Practitioners, OB/GYN, Internist, and Physician Assistant at busy Migrant/Community Clinic in Grandview, Washington. Full-range Family Practice, including Obstetrics, hospital work, and Emergency coverage. Excellent relationship with well trained BC Family Practitioners and surgeon in community. Friendly rural area with good schools. Close to mountain recreational areas and water sports. Professional liability paid. Excellent benefits, vacation liberal. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

PEDIATRICIANS—Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

BE/BC UROLOGIST to join busy 28 doctor multispecialty group practice. Excellent practice opportunity, full range of benefits, early partnership status. For more information contact Shane Spray, 1400 Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

NEED ASSOCIATE to join busy dermatology practice in Santa Barbara, California. Will also consider sale at a reasonable price. Excellent opportunity to live in a beautiful seaside community. Call Dr Senn at (805) 569-0186 or evenings at (805) 565-3908.

PHYSICIANS WANTED

PHYSICIAN OPPORTUNITIES NATIONWIDE
For all specialities for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **G & G Physician Services, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call (800) 727-2478, FAX (408) 727-7390.** Never a fee to the physician.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

CALIFORNIA MULTISPECIALTY. Dermatologist, Radiologist, Otorhinolaryngologist, General Surgeon, Cardiologist, Internal Medicine, Pediatrician, Gastroenterologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

OB/GYN—Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE Physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

BC/BE OB/GYN with commitment to caring for the underserved, needed to join 13 physician (OB, Family Practitioner, Pediatrics, Internal Medicine) Primary Care community health clinic in Toppenish, Washington. Rural setting, beautiful, sunny, central Washington near Columbia River gorge. Diverse cultural influences (Hispanic and Native American). Recreational opportunities including fishing, skiing, and bikers' paradise. Competitive salary with excellent benefit package including vacation up to 32 days per year and paid professional liability. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

NEPHROLOGIST WANTS PARTNER/ASSOCIATE BC/BE Gastroenterologist/Cardiologist/Nephrologist/Pulmonologist. Excellent practice, equal partnership opportunity without buy-in or overhead. Send CV to Dr M. Streger, 27800 Medical Center Rd, Ste 122, Mission Viejo, CA 92691.

MAJESTIC SKAGIT VALLEY IN WESTERN WASHINGTON has multispecialty group seeking eighth Family Practitioner. BE/BC, OB optional. Competitive salary and benefits. If interested, send CV to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

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PHYSICIANS WANTED

EXECUTIVE MEDICAL DIRECTOR
INDUSTRIAL MEDICAL COUNCIL
CALIFORNIA DEPARTMENT OF INDUSTRIAL RELATIONS

Plan, organize, direct the work of the staff of the Industrial Medical Council (IMC).

Applicants must hold a physician's and surgeon's certificate granted under Chapter Five of the California State Business and Professions Code and have a minimum of two years experience with workers' compensation performing consultations or exams, or the equivalent of four years experience in industrial medicine including direct treatment of occupational injuries and illness.

Position appointed by the IMC (exempt from civil service) and eligible for similar benefits provided to civil service classes.

Send résumé and salary history to:

Industrial Medical Council
c/o Gayle A. Walsh, Secretary
630 Fountain Ave
Pacific Grove, CA 93950

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NORTHERN CALIFORNIA

Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

PHYSICIANS WANTED

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full-/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

BEAUTIFUL OREGON COAST. Private multispecialty cooperative with excellent facility seeking Family Practice physician to join five full-time Family Practitioners. Full spectrum of Family Practice. In-house lab, x-ray, day surgery. Contact Marce Knight, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294 or (800) 234-1231.

PEDIATRICIAN BC/BE for hospital-based teaching practice. Interest and training in Neonatology and Critical Care Pediatrics preferred. Join three full-time Pediatricians and two full-time Neonatologists in hospital with Community Level III NICN and busy inpatient and outpatient services. Paid malpractice. Salary negotiable based on training and experience. Submit CV and references to Leedell Reuben, MD, Director, Pediatrics/Neonatal Services, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201, (209) 468-6611. AA/EOE.

POSITIONS AVAILABLE FOR EMERGENCY PHYSICIANS WORKING PM SHIFTS. Hourly differential paid in addition to fee-for-service compensation. Shifts vary from seven to nine hours in length. Excellent fringe benefits. Malpractice paid. Contact Nancy C. Kendall at SPEMG, Inc, 8350 Auburn Blvd, Ste 100, Citrus Heights, CA 95610; or call (916) 727-1049 for more information.

BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

BC/BE GENERAL INTERNIST NEEDED. Nine physician department in 27 doctor multispecialty clinic. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

FOURTH INTERNIST/FAMILY PRACTICE MD for well loved multidisciplinary health center part of east San Francisco bay area community clinic network. 24 plus clinic hours plus share hospital call and coverage. Resident teaching and UCSF clinical affiliation possible. Call (510) 644-6060.

SEATTLE, WASHINGTON. PACIFIC MEDICAL CENTER has Family Practitioner positions, BC/BE, available at three of its six neighborhood clinics. PMC is a growing, Primary Care-based, multispecialty organization with extremely well run, well equipped clinics that provide many ancillary services. Most of the clinics are located within one mile of a major hospital. PMC offers its providers a balanced life-style, competitive salaries, and an excellent benefit package that includes paid malpractice. The greater Seattle area offers year-round outdoor recreation including, skiing (snow/water), hiking, boating, and fishing at numerous lakes, national parks, and in Puget Sound. Send CV to Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4100.

AMBULATORY CARE, Hayward, Modesto, Orange County, California. Thriving practices, attractive facilities, competitive salary, profit-sharing, partnership with growth potential. Contact Robin Morgan, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612; (510) 835-7431. Outside of California, (800) 842-2619.

OCCUPATION MEDICINE. Strong knowledge of Orthopedics. Prestigious and busy clinic with triple coverage. Beautiful facility, great staff. No call, no weekends. Work Net, PO Box 26692, Salt Lake City, UT 84199.

PHYSICIANS WANTED

NORTHERN CALIFORNIA—FAMILY PRACTICE FACULTY. Vigorous, growing program with rural emphasis, in Shasta-Cascade recreation area seeks residency trained BC/BE Family Physician to join core faculty team. Practice, teaching, and OB experience desirable. Responsibilities include teaching and direct patient care in hospital, FPC and coordination of R-1 curriculum. UC Davis affiliate program trains 18 residents in 254-bed regional referral center. Clean air, good schools, four-season recreation. Send CV to Perry Pugno, MD, Program Director, 2615 Breslauer Wy, Redding, CA 96001; (916) 246-5716.

NORTHERN CALIFORNIA-FACULTY INTERNIST. Vigorous, growing Family Practice residency with rural emphasis in Shasta-Cascade recreation area seeks residency trained BC/BE Internist to join core faculty team. Practice and teaching experience desirable. Responsibilities include teaching and direct patient care in hospital and clinic. Clinical research encouraged. UC Davis affiliate program trains 18 residents in 254-bed regional referral center. Clean air, good schools, four-season recreation. Send CV to Perry A. Pugno, MD, Program Director, 2615 Breslauer Wy, Redding, CA 96001; (916) 246-5716.

GENERAL PHYSICIANS AND INTERNISTS— Physicians' salary to $70,020. Internists' (BE/BC) salary to $77,280. Western State Hospital is a fully accredited (JCAHO) and certified (HCFA) hospital. The hospital is associated with the University of Washington Medical School with clinical faculty appointment possible. A research institute, with the University, is now being developed. Western currently has a physicians' staff of 59, including 37 Psychiatrists and 22 other nonpsychiatric positions. Excellent benefits, including hospitalization/medical insurance, retirement, vacation estimated equivalence at 24%, plus optional deferred income plan. Send CV to Jerry L. Dennis, MD, Acting Medical Director, Western State Hospital, Fort Steilecoom, WA 98494; (206) 756-2349. EOE.

INTERNIST. BE/BC Internist wanted as associate for solo practitioner in San Luis Obispo County. Growing medical community offering a tremendous quality of living; award winning local wineries, recreational lakes and beautiful oak-studded hillsides. Income guarantee. Contact Steven J. McAllen, MD, 959 Las Tablas Rd, Ste B2, Templeton, CA 93465; phone (805) 434-1166.

COASTAL CALIFORNIA. San Luis Obispo, Internal Medicine BC/BE, busy multispecialty group, eight miles to beach, excellent schools, recently rated "best small town in USA." Rewarding hospital-based practice. Guaranteed salary, malpractice covered, excellent call rotation. Call or send CV to Fran Wolke, San Luis Obispo General Hospital, PO Box 8113, San Luis Obispo, CA 93403-8113; (805) 549-4936.

OUR MULTISPECIALTY CLINIC IS LOCATED WITHIN ONE HOUR OF SEATTLE. Due to the high population growth in our service area we have opportunities for the following specialties: Family Practice, Internal Medicine, OB/GYN, Otolaryngology, and Dermatology. We offer independent practice ownership with income guarantees during start-up. Ancillary services and surgery center on campus. Good specialty mix. Well regarded for quality patient care. Please call D. M. Knight and Associates, Inc for more information and/or brochure; (206) 842-6319.

GENERAL INTERNIST in the Pacific Northwest. Busy 30 physician multispecialty group practice looking for General Internist with ICU skills and interests to join existing Internal Medicine department. Competitive salary and benefits. Send CV to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

SALT LAKE CITY—URGENT CARE/FAMILY PRACTICE. Six year old center in upper middle class community. BC preferred, early partnership available. Great recreation area. Work Net, PO Box 26692, Salt Lake City, UT 84199.

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PHYSICIANS WANTED

INTERNAL MEDICINE, FAMILY PRACTICE, URGENT CARE, OB/GYN, AND ACADEMICS

Positions in large metropolitan cities, urban, and rural communities with a concentration in the Great Lakes area and Plains States. Whether you prefer a cosmopolitan lifestyle, a city surrounded by nature and the beauty of four seasons, the peaceful rolling farm country, or perhaps life in historic villages—there is something for everyone. To discuss your practice preferences and these opportunities, please call our toll-free number, (800) 243-4353, or send your CV to STRELCHECK & ASSOCIATES, INC, 10624 N. Port Washington Rd, Mequon, WI 53092.

NORTHERN CALIFORNIA'S NUMBER ONE IMMEDIATE CARE medical center is currently seeking a motivated physician with Emergency/Family Practice experience to join our team. A college town, very attractive compensation, and location, are just a few of the things that make this position unbeatable. Please contact Francine Marquis; (916) 891-1676, 376 Vallombrosa Ave, Chico, CA 95926.

CHAIRPERSON, DEPARTMENT OF MEDICINE, Santa Clara Valley Medical Center, San Jose, California. We invite applications for Chair of the Department of Medicine. SCVMC is a 350-bed public teaching hospital operated by the County of Santa Clara and affiliated with Stanford University School of Medicine. Our major departmental missions are to provide excellent care to patients and to educate students, residents and fellows. We have 46 house staff in both categorical and primary care tracks. The department has 11 divisions with 40 full-time faculty, and is supported by a vigorous administration. We seek an individual with the following qualifications: BC in Internal Medicine, proven administrative ability, experience in program management and development, and recognized teaching ability. Submit applications and CV to Search Committee for Medicine, Attn: Kent Imai, MD, Department of Medicine, Santa Clara Valley Medical Center, 750 S. Bascom Ave, San Jose, CA 95128. AA/EOE.

WANTED: BC GENERAL OR SUBSPECIALTY SURGEON to fill the position of Chief of Surgery at a 181-bed county hospital and large ambulatory care system located in the San Francisco bay area. Responsibilities include teaching the 27 residents of the hospital-based, UC Davis-affiliated Family Practice Residency Program; assisting in the development of the Family Practice faculty; general clinical and administrative duties; and the clinical and administrative supervision of the general and subspecialty surgeons. Salary and benefits negotiable. Please send CV to Steven Tremain, MD, Director of Medical Staff Affairs, Merrithew Memorial Hospital, 2500 Alhambra Ave, Martinez, CA 94553; phone (510) 370-5110; FAX (510) 370-5142. EOE.

BC/BE OB/GYN to join one Internist, one Family Nurse Practitioner, one Pediatric Nurse Practitioner, and one OB/GYN Nurse Practitioner in Walla Walla, Washington. Shared call with two local OB/GYNs. Competitive salary, excellent benefit package, including vacation up to 32 days per year and professional liability. Public Health Service immediate loan repayment slot. Contact Sylvia Arroyo, Clinic Administrator, Family Medical Center, PO Box 515, Walla Walla, WA 99362; (509) 525-6650, or Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant; (509) 865-5898.

FULL-TIME EMERGENCY PHYSICIANS to join a Level 11 trauma center. Active practice, 39,000 visits annually. Double coverage 24 hours with additional physician coverage during peak hours. Opportunities available for administrative, teaching, and prehospital direction. Located in urban community with significant cultural, recreational, and education resources available. Send CV to Director, PO Box 80412, Phoenix, AZ 85060-0412.

PHYSICIANS WANTED

NORTHERN CALIFORNIA

Outstanding practice opportunities due to healthcare services expansion for Family Practice, Internal Medicine, OB/GYN, Anesthesiology, Cardiology, and Pediatrics in a small, but rapidly growing community 40 miles north of Sacramento. Location offers year around recreation and is centrally located within short driving distance to San Francisco, Lake Tahoe, Napa Valley, and Mendocino coast. Please contact Director of Physician Recruitment, Rideout Memorial Hospital, 726 Fourth St, Marysville, CA 95901; telephone (916) 749-4407.

JACKSON, WYOMING. Emergency Department position available. New hospital, good specialty staff, good recreation. Scott Thomas, MD, Box 1776, Rawlins, WY 82301; (307) 324-7191.

SAN JOSE. Multispecialty Primary Care group practice needs BC/BE physicians for Family Practice, Pediatrics, Internal Medicine and OB/GYN. Generous salary, benefits, and livable practice schedule are offered to qualified candidates. Affiliation with progressive 200-bed hospital. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411; FAX (415) 399-0411.

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as *locum tenens* statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **Western Physicians Registry: Northern California, contact Jim Ellis, Director, (510) 601-7676 or (800) 437-7676. Southern California, contact Tracy Zweig, Director, (805) 643-9346 or (800) 635-3175.**

PRACTICES AVAILABLE

SAN DIEGO COUNTY. Family, Internal, OB/GYN, and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

NORTHERN CALIFORNIA SAN JOAQUIN VALLEY. Urban Family Practice for sale. $650,000 gross. Will help with transition. Inquire at PO Box 40, French Camp, CA 95231.

SAN DIEGO EAST COUNTY—General medical adult practice. Gross $230,000 on four days per week. Seller to retire. Low overhead, net cash flow 50% of gross. Computerized within office automated lab. Excellent personnel. 99% unadjusted collection rate. Broker—Practice Consultants; (619) 528-2321.

PRACTICE FOR SALE. Five Year Hematology/Oncology practice in northern Utah. Service area of 100,000 plus. Gross $400,000. Seller retiring. Safe place to raise family. Year round outdoor activities. Send inquiries to Box 260, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120.

AVAILABLE FOR SALE. General Surgery, hospital based practice. Colorado Springs, Colorado. 25 E Jackson, Ste 305, Colorado Springs, CO 80907; (719) 636-0075; FAX (719) 636-0070. Sale includes Penrose Hospital office lease, equipment, patient records, managed care contacts, and referral base.

NEPHROLOGY/INTERNAL MEDICINE—SAN DIEGO AREA. Mature, well established quality practice with dialysis units. Average net cash stream over $400,000. Seller to retire in one year. Broker—Practice Consultants; (619) 528-2321.

FOR SALE. Established, busy Urology practice in southwestern New Mexico. No investment required. Excellent year 'round climate and outdoor recreational opportunities. Call collect, Pierson Deming, MD (505) 388-1561 (office) or (505) 388-4557 (home): or call Steve Jacobson, Administrator, Gila Regional Medical Center, (505) 388-1591.

PRACTICES AVAILABLE

WEST LOS ANGELES RADIOLOGY PRACTICE. Established 30 years. Good location. 319K (Gross 1990). Will assist in transition. Inquiries to Lee, 15237 Sunset Blvd, #12, Pacific Palisades, CA 90272.

CALIFORNIA COASTAL SOLO ENT PRACTICE. Established 12 years. Three exam rooms, minor or, audio, surgical equipment, fully computerized. Available summer 1992, leaving for fellowship. Reply to Box 262, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BUSY GYNECOLOGIST READY TO RETIRE. Anaheim, California. This is a cream of the crop practice. Inquiries to Janet Parry, RN, PPP Medical Practice Sales, 1801 W Romneya, Ste 601A, Anaheim, CA 92801; (714) 991-8111.

ENT AND RELATED PLASTIC SURGERY near Beverly Hills. Very good area for this type of practice. Solo practice grossing $500K—net plus/minus 50%. Most revenue is PI or WC. Very little hospital surgery. Equipment cost over $100K. Other Southern California practices include Family Practice, Allergy, Psychiatry, etc. If you're a buyer call us . . . We'll talk. The Oak Tree Associates; (714) 855-6566, (800) 233-0659.

OFFICE SPACE

MARIN COUNTY-GREENBRAE. Small, attractive office in busy building near Marin General Hospital. Excellent location. (415) 461-2100.

SAN FRANCISCO—Stonestown Medical-Dental Building. Established facility with good referrals. Adjacent to Stonestown Galleria at 19th Avenue. Excellent public transportation and free parking. Call (415) 564-8848.

UROLOGY OFFICE TO SHARE OR SUBLEASE. Next to Medical Center of Tarzana. Well equipped, attractively decorated. Ground floor. Free parking. 1800 square feet. (818) 996-6011; in California (800) 675-1977.

OFFICES FOR LEASE OR RENT: PETALUMA, SAN FRANCISCO, NORTH BAY. Pediatrician, OB/GYN, General Medicine/Internal Medicine. Opportunity for quality oriented practitioner to establish practice in this highly desirable, growing, family-oriented community of approximately 50,000 population, in upscale new medical/dental building. Excellent potential referral sources. Location near community hospital. For information contact William Conrow, DDS, 1430 E. Washington St, Petaluma, CA 94954; (707) 762-0067.

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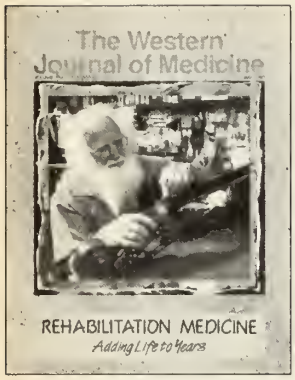

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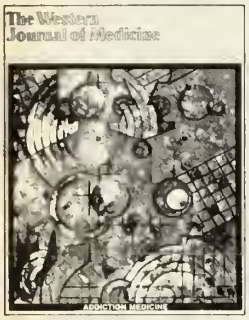

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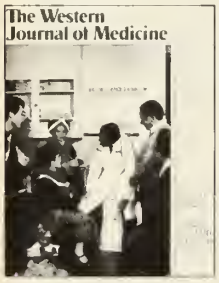

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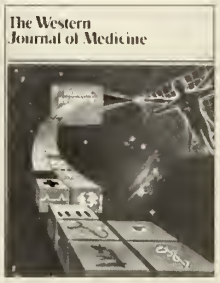

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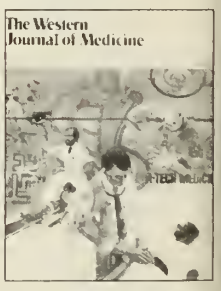

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(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, tight-resistant containers as defined in the USP/NF.

July 1990

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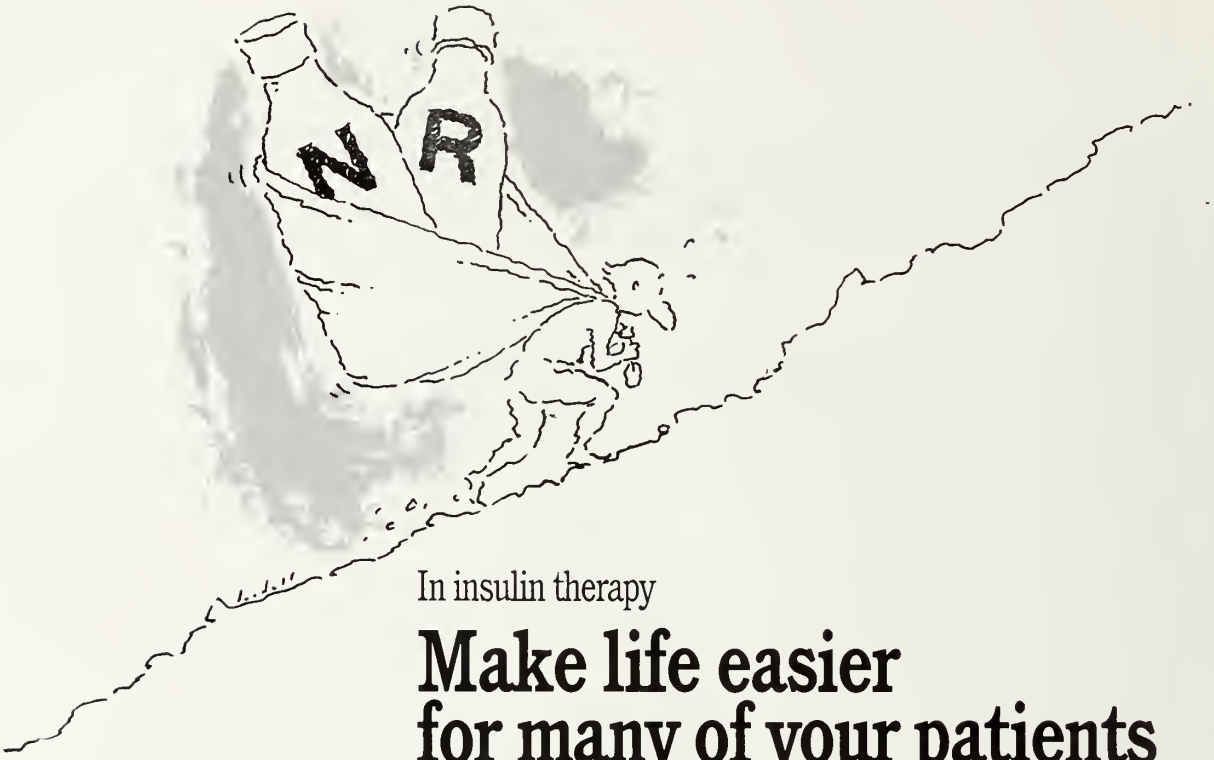

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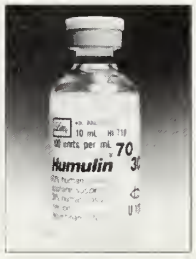

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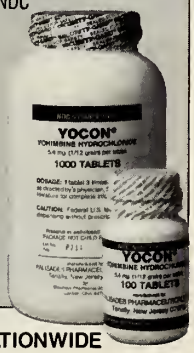

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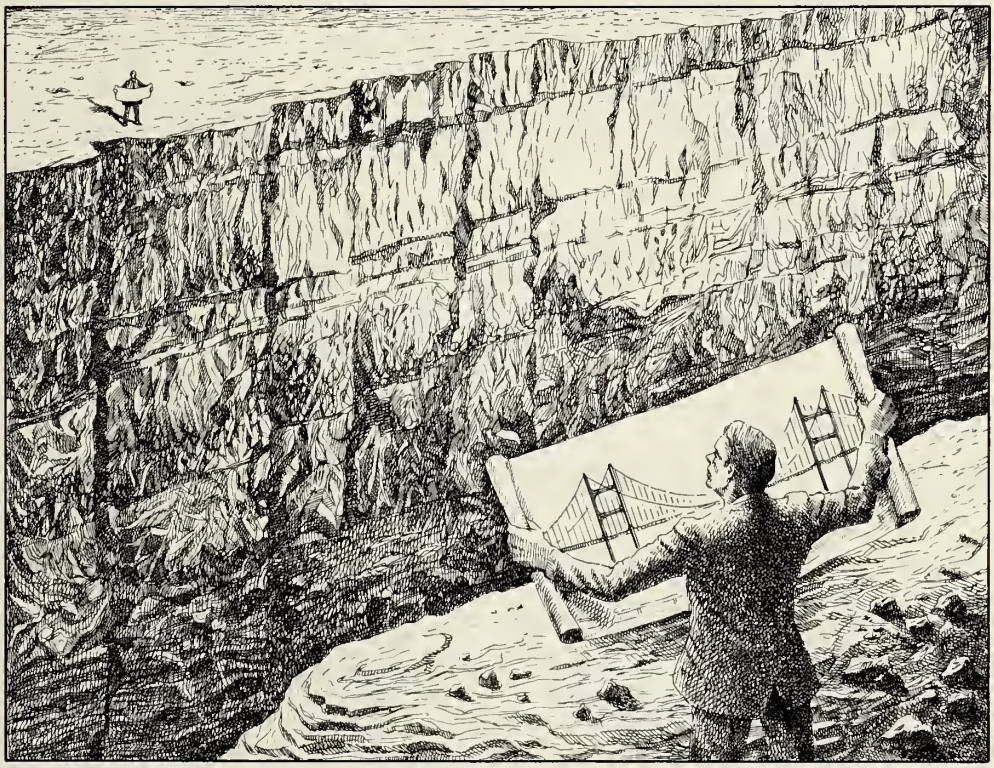

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‡Verapamil should be administered cautiously to patients with impaired renal function.

References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade: Verapamil in Focus.* New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol.* 1990;66:131-151. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow-release verapamil in essential hypertension. *Eur J Clin Pharmacol.* 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation.* 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology.* 1988;39:1025-1029.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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Address medical inquiries to:
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Medical & Scientific Information Department
4901 Searle Parkway
Skokie, IL 60077

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FROM BRISTOL-MYERS SQUIBB

A NEW DIRECTION IN LIPID MANAGEMENT

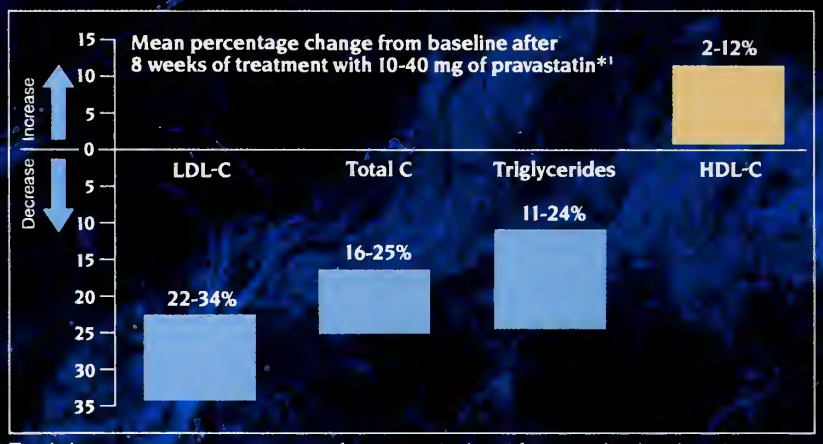
PRAVACHOL™

pravastatin sodium 20 mg tablets

Effective

cholesterol control

- Consistently and significantly reduces total C and atherogenic LDL-C; positively affects other key lipids



*Each bar represents a range of means derived from a single placebo-controlled study that included 55 patients treated with pravastatin.

PRAVACHOL® (pravastatin sodium) is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Safety

profile promotes confidence

- Prescribed for more than 1,200,000 patients worldwide[2]
- Studied in over 14,000 patients in clinical research[2]

Well tolerated...

a side-effect profile generally comparable to placebo

Adverse clinical events attributed to study drug:	PRAVACHOL® (n=900)	Placebo (n=411)
Headache	1.7%*	0.2%
Nausea/vomiting	2.9	3.4
Diarrhea	2.0	1.9
Abdominal pain	2.0	3.9
Constipation	2.4	5.1
Flatulence	2.7	3.4
Heartburn	2.0	0.7
Cardiac chest pain	0.1	0.0
Rash	1.3	0.9
Fatigue	1.9	1.0
Chest pain	0.3	0.2
Dizziness	1.0	0.5
Urinary abnormality	0.7	1.2
Rhinitis	0.1	0.0
Cough	0.1	0.0
Localized pain	1.4	1.5
Myalgia	0.6	0.0

*Statistically different from placebo.

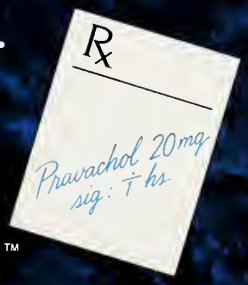
- Discontinuation rate from pravastatin (1.7%) was not statistically different from that of placebo (1.2%)

Nighttime dosing

with or without food

Usual dose: 20 mg tablet once daily at bedtime.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the last page of this advertisement.



PRAVACHOL™

pravastatin sodium 20 mg tablets

References: 1. Jones PH, et al Once-daily pravastatin in patients with primary hypercholesterolemia a dose-response study. *Clin Cardiol.* 1991;14 146-151 2. Data on file, Bristol-Myers Squibb.

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS)

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY, Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (< 0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS, Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (1½) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS, Skeletal Muscle.

Antipyrine. Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION, Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine. The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL), *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Other Drugs. During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥ 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p < 0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area ($mg/meter^2$). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS, General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class.

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions. An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS, Skeletal Muscle and PRECAUTIONS, Drug Interactions.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. (J4-422A)

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0542-508 Issued May 1992

Bristol-Myers Squibb Company

What Is A Single-handed Approach To Blood Pressure Reduction

In Many Patients:

One Agent

Once-A-Day*

One Price

One price for all tablet
strengths... 10 mg, 20 mg, 40 mg.

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

Accupril is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

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ONCE-A-DAY*

ACCUPRIL

quinapril HCl tablets 10, 20, 40 mg

A Single-handed Approach To Blood Pressure Reduction

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ACCUPRIL should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Before prescribing, please see full prescribing information. A brief summary follows.

INDICATIONS AND USAGE
ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS
ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS
Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).**

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ACCUPRIL as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, ACCUPRIL should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. Removal of ACCUPRIL, which crosses the placenta, from the neonatal circulation is not significantly accelerated by these means.

No teratogenic effects of ACCUPRIL were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 180 times (in rats) and one time (in rabbits) the maximum recommended human dose.

PRECAUTIONS
General
Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent, and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients
Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions
Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:
- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m² basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro* chromosome aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m², respectively).

Pregnancy
Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS, Fetal/Neonatal Morbidity and Mortality

Nursing Mothers
It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use
Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use
The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS
ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below:

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

See PRECAUTIONS, Cough.

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Fetal/Neonatal Morbidity and Mortality
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings
Hematology: (See WARNINGS)
Hyperkalemia: (See PRECAUTIONS)
Creatinine and blood urea nitrogen: Increases (71.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

*In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

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Those interested in taking part in this unique CME program should contact Amy Wright in CMA's Department of Physician Education at 415/882-5186.

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Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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CARDIOLOGY

July 26-August 1—**Current Concepts in Cardiology.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 19 hrs. Contact: UCD.

August 13-15—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $325-$425. Contact: UCSF.

September 12—**Stress Echocardiography.** Sutter Health at Hyatt Regency, Sacramento. Sat. Contact: Sutter Health, (916) 733-3883.

September 25—**Primary Care Issues in Cardiovascular Disease.** Alta Bates Medical Center at Medical Center Auditorium. Fri. 7 hrs. $75. Contact: Mary Grim, (510) 204-1420.

September 25-26—**Coronary Interventions: 1992.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sat. 14 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 1-3—**Cardiology Update—1992.** UCSF at Quail Lodge, Carmel. Thurs-Sat. 11 hrs. $445. Contact: UCSF.

DERMATOLOGY

July 14-18—**Dr. Hugh Greenway's Eighth Annual Conference: Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation at UCSD Campus and Scripps Clinic, La Jolla. Wed-Sat. 36 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

July 30-August 1—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 24 hrs. $425. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla. (619) 554-8556.

August 10-12—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 17-18—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Sat-Sun. Contact: UCSF.

EMERGENCY MEDICINE

June 22-26—**Emergency Medicine Symposia III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. Contact: UCSD.

June 26-27—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Anaheim. Fri-Sat. 15 hrs. $295-$495. Contact: Kathy Hester, (800) 451-7475.

August 17-21—**Emergency Medicine Symposia II.** UCSD at Basic Science Building. Mon-Fri. Contact: UCSD.

August 19-23—**Wilderness Medicine: 1992.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $395. Contact: Gene Allred, MD, PO Box 321, Yreka 96097. (800) 888-5632.

October 2-3—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Marina Del Rey. Fri-Sat. 15 hrs. Contact: Kathy Hester, (800) 451-7475.

October 10—**Emergency Medicine.** Sutter Health at Sheraton Sunrise, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

October 19-23—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

October 26-30—**21st Annual Topics in Emergency Medicine.** UCSF at Ritz-Carlton, San Francisco. Mon-Fri. 32 hrs. $560. Contact: UCSF.

October 29-November 1—**14th Year Biannual Wound Management Workshop.** UCSD at La Jolla Marriott. Thurs-Sun. 18 hrs. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

November 9-13—**Emergency Medicine Symposia III.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

June 15-20—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Marriott Hotel, Newport Beach. Mon-Sat. Contact: UCI.

June 18-21—**Office Gynecology: Primer for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 18 hrs. $188-$325. Contact: UCLA Extension.

June 27—**Perspectives on Primary Care.** Saddleback Memorial Medical Center at Dana Point Resort. Sat. 4 hrs. Contact: Ivana Jeric, 24451 Health Center Dr, Laguna Hills 92653. (714) 472-7097.

July 6-9—**Family Practice Board Review Course.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

July 30-August 2—**Orthopedics for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 20 hrs. $206-$375. Contact: UCLA Extension.

August 7-9—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 21-23—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 21-23—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Loews Coronado Bay Resort, Coronado Island, San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 23-25—**7th Annual Primary Care Medicine: Principles and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 15 hrs. $485. Contact: UCSF.

September 25—**Primary Care Issues in Cardiovascular Disease.** Alta Bates Medical Center at Center Auditorium Fri. 7 hrs. $75. Contact: Mary Grim, (510) 204-1420.

October 15-18—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Maui Inter-Continental Hotel, Hawaii. Thurs-Sun. 16 hrs. $281-$375. Contact: UCLA Extension.

GERIATRICS

June 1992—**Health Aspects of Aging: Promoting Health and Preventing Disability.** UCLA at School of Public Health. Tuesdays. $225. Contact: UCLA.

November 16-18—**Geriatrics Update—1992.** Sharp Memorial Hospital at Loew's Coronado Bay Resort. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INFECTIOUS DISEASES

September 19—**AIDS.** Sutter Health at Sacramento Inn. Sat. Contact: Sutter Health, (916) 733-3883.

November 13-15—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

June 22-26—**20th Annual Advances in Internal Medicine.** UCSF at Cole Hall Parnassus Campus. Mon-Fri. 32 hrs. $610. Contact: UCSF.

August 23-28—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. 25 hrs. $480. Contact: UCD.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 598)

August 29-September 3—**10th Comprehensive Nephrology Review Course.** UCLA at Beverly Hilton Hotel, Beverly Hills. Sat-Thurs. 51 hrs. $850. Contact: UCLA Extension.

September 17-19—**American Gastroenterological Association 1992 Fall Postgraduate Course.** AGA at Westin St. Francis, San Francisco. Thurs-Sat. Contact: SLACK Inc, 6900 Grove Rd, Thorofare, NJ 08086-9447. (609) 848-1000.

November 5-7—**Otolaryngology Update: 1992.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. $395. Contact: UCSF.

November 10-14—**VIIth International Symposium on the Biology of Vascular Cells.** Scripps Clinic and Research Foundation at Princess Resort Mission Bay, San Diego. Tues-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

NEUROLOGY

July 30-August 1—**New Advances in Common Neurological Disorders.** UCSD at Catamaran Hotel, San Diego. Thurs-Sat. Contact: UCSD.

October 23-24—**Transcranial Doppler and Cerebral Blood Flow Monitoring: Applications in Neurology, Neurosurgery and Anesthesiology.** UCLA at Sheraton Miramar Hotel, Santa Monica. Fri-Sat. Contact: UCLA Division of Neurosurgery, (310) 206-0626.

OB/GYN

July 26-29—**5th Annual In Vitro Fertilization and Embryo Transfer: A Comprehensive Update—1992.** UCLA at Four Seasons Biltmore Hotel, Santa Barbara. Sun-Wed. 20.5 hrs. $400-$522. Contact: UCLA Extension.

July 29—**10th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Wed-Sat. Contact: UCI.

October 3-4—**Ultrasound Update: 1992.** UCD at Sacramento. Sat-Sun. Contact: UCD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

OCCUPATIONAL/ENVIRONMENTAL

July 26-31—**Sports Medicine.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

October 19-30—**Occupational and Environmental Medicine: Session II.** UCSF at Miyako Hotel, San Francisco. 1½ wks. 80 hrs. $1,400. Contact: UCSF.

November 2-6—**Advances in Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

ONCOLOGY

October 12-18—**18th Annual Lukes Lymphoma Conference.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Sun. 25 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-6310.

October 24—**Melanoma and Pigmented Lesions.** Stanford University Medical Center at Fairchild Auditorium, Stanford. Sat. Contact: STAN.

October 26-28—**16th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Meeting Management, Cancer Symposium, 5665 Oberlin Dr, # 110, San Diego 92121. (619) 453-6222.

November 5-8—**Prostate Cancer.** Sutter Health at Hyatt Regency, Sacramento. Thurs-Sun. Contact: Sutter Health, (916) 733-3883.

OPHTHALMOLOGY

July 29-August 2—**Summer Institute.** American Academy of Ophthalmology at Sheraton Palace Hotel, San Francisco. Wed-Sun. $325-$500. Contact: Sarah Samuels, (415) 561-8515.

September 10-13—**Uveitis and Retinal Frontiers.** UCSF at Carmel Valley Ranch Resort. Thurs-Sun. Contact: UCSF.

October 10—**Ophthalmology Update: 1992.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

ORTHOPEDICS

June 14-19—**16th Annual Fingers to the Toes.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 28 hrs. $510. Contact: UCD.

October 31—**Orthopedics Symposium.** Sutter Health at Sheraton Sunrise, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

November 5-6—**Low Back Pain and Its Relation to the Sacroiliac Joint.** UCSD at San Diego Convention Center. Thurs-Fri. 12 hrs. $335. Contact: UCSD.

PATHOLOGY

August 7-8—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD at La Jolla. Fri-Sat. 15 hrs. Contact: Daniel Gormley, MD, 412 W Carroll Dr, Ste 207, Glendora 91740. (818) 963-7684.

August 9-15—**12th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton, Mauna Lani Kohala Coast, Big Island of Hawaii. Sun-Sat. 27 hrs. $950. Contact: UCSF.

October 10—**Fine Needle Aspiration: Advanced Tutorial XXI.** UCSF. Sat. 12 hrs. $650. Contact: UCSF.

October 17—**32nd Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Irvine Marriott. Sat. Contact: Sylvie Tarro, (310) 641-8152.

PEDIATRICS

June 26-28—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. Contact: Continuing Education, (619) 576-4072.

July 13-22—**Lactation Management Education Program.** UCSD. 1½ wks. Contact: UCSD.

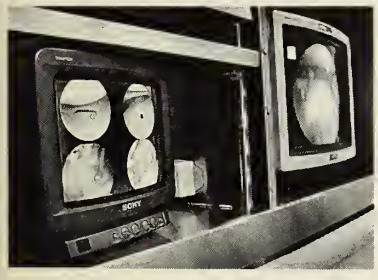
July 17-August 5—**Lactation Management Education Program.** UCSD. 1½ wks. Contact: UCSD.

August 24-26—**Pediatrics Update: 1992.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 682)

LET ME TELL YOU ABOUT THE FIRST TIME I WAS ON TELEVISION.

As a family practice physician, Dr. Alvin Sockolov had assisted in operating room number 7 at Sutter General Hospital many times. But after re-injuring his knee, there he was, undergoing ACL surgery at the hands of Dr. David Coward. While choosing surgery was a difficult decision, choosing Sutter General was not. "Dr. Coward prefers to operate at Sutter General," says Dr. Sockolov. "A surgeon needs special equipment, fine instruments, and a capable staff to feel comfortable. Sutter General has what physicians need for procedures to run smoothly." More orthopedic surgeries are performed at Sutter General Hospital than at any other hospital in the region. Advanced diagnostic equipment, specially trained orthopedic nurses, and a team of rehabilitation specialists all help give Sutter General a reputation that's unmatched in Northern California. In addition, educational programs, a health library, outpatient and extended care facilities provide both physicians and patients with the best resources available. "The only problem I had with Sutter General," says Dr. Sockolov, "was that when it came time to leave, I didn't want to go. Everything was top-notch." For more information about available services, call Sutter Orthopedic Center at Sutter General Hospital in Sacramento, (916) 733-8880.



Alvin Sockolov, M.D.

Sutter Orthopedic Center
SUTTER GENERAL HOSPITAL

ABSTRACTS JUNE 1992

(Katsufrakis PJ, Radecki SE: Clinical training in human immunodeficiency disease for community physicians—The Los Angeles experience. West J Med 1992 Jun; 156:619-623)

In the past decade, the increased number of persons being treated for infection with the human immunodeficiency virus (HIV) has placed an enormous burden on specialty clinics. This is especially true in Los Angeles, where care of patients with the acquired immunodeficiency syndrome (AIDS) has been termed a "crisis" situation. Especially in its early stages, HIV disease can be appropriately managed by primary care physicians who provide patients with medical and psychological counseling and refer them to specialists when major AIDS-related complications develop. Physicians completing their training as recently as 5 years ago, however, received little systematic preparation in the care of HIV-infected patients and thus may lack important skills such as the ability to recognize opportunistic infections early in their course. By means of a 1-week intensive preceptorship in a high-volume AIDS clinic, we are preparing community physicians to assume a more active role in providing care for this growing patient population. In the preceptorship, participants receive one-on-one training from specialists in infectious diseases, pulmonary diseases, and hematology and oncology, as well as from internists and family physicians.

Evaluation of the clinical experience demonstrated a greater level of confidence on the part of program participants in treating HIV-infected patients and showed that participants screen and test high-risk patients in their practices and devote a substantial proportion of their practices to caring for HIV-infected patients.

HIV DISEASE
PHYSICIAN TRAINING
AIDS
ACQUIRED IMMUNODEFICIENCY SYNDROME
HUMAN IMMUNODEFICIENCY VIRUS

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Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

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WHEN DEPRESSION KEEPS YOUR PATIENTS OUT OF THE MAINSTREAM

MOVE FORWARD WITH CONFIDENCE

ONCE-A-DAY

NEW **Zoloft**™

(sertraline HCl) 50 mg, 100 mg scored tablets

Please see brief summary of prescribing information on last page of this advertisement.

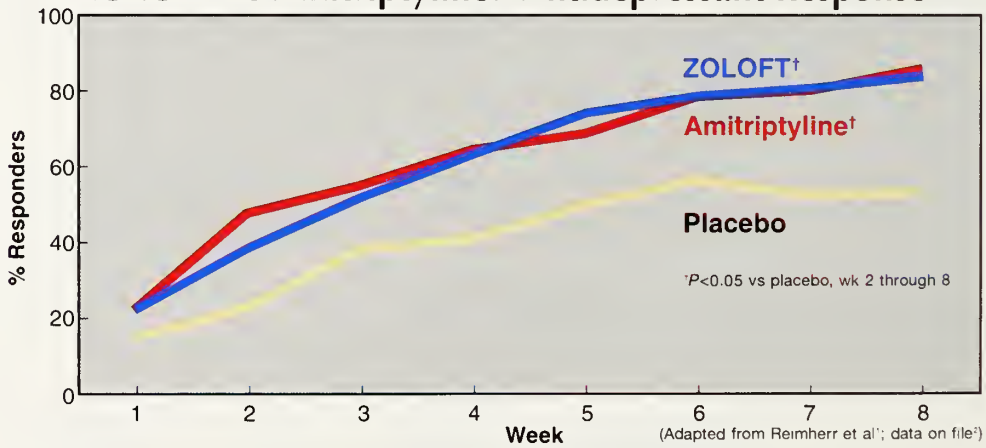
NOW, IN DEPRESSION MANAGEMENT...

GETS DEPRESSED PATIENTS BACK INTO THE MAINSTREAM

- ZOLOFT, a new selective serotonin reuptake inhibitor, improves mood and enhances patients' ability to function
- ZOLOFT effectively reduces depressive symptoms, which may include dysphoric mood, loss of interest or pleasure, increased fatigue, and psychomotor agitation or retardation

ZOLOFT...Effective in the Treatment of Depression

ZOLOFT vs Amitriptyline: Antidepressant Response*[1,2]



(Adapted from Reimherr et al[1]; data on file[2])

*Observed cases, evaluable patients (ie, patients who took drug on or after double-blind treatment day 11 and who had efficacy evaluations within that same time frame); response is defined as a CGI-Improvement score of 1 (very much improved) or 2 (much improved) at time point. Patient numbers for each regimen: ZOLOFT—wk 1=117, wk 2=120, wk 3=106, wk 4=98, wk 5=93, wk 6=94, wk 7=83, wk 8=80; amitriptyline—wk 1=116, wk 2=113, wk 3=111, wk 4=104, wk 5=102, wk 6=92, wk 7=89, wk 8=76; placebo—wk 1=124, wk 2=120, wk 3=116, wk 4=108, wk 5=97, wk 6=89, wk 7=94, wk 8=85.

Double-blind, multicenter, placebo-controlled, parallel study of antidepressant effects of ZOLOFT vs amitriptyline in 448 subjects who met DSM-III criteria for major depression. Symptoms were assessed after a single-blind, 7-day to 14-day placebo washout. Patients were randomly assigned to ZOLOFT, amitriptyline, or placebo for 8 wk. Daily dosage ranges: ZOLOFT—50-200 mg; amitriptyline—50-150 mg.

© 1992, Pfizer Inc

ZOLOFT...Effective Continuation Therapy[2,3]

- Responders to ZOLOFT during an 8-week acute-treatment phase were randomized to continue on ZOLOFT or placebo
- A significantly lower relapse rate* was observed for patients treated with ZOLOFT compared with those on placebo, in an assessment of the first 8 weeks of the continuation period
- The effectiveness of ZOLOFT has not been systematically evaluated in long-term use for more than 16 weeks

ZOLOFT...Physician and Patient Confidence

- Low risk of toxicity in overdose
- ZOLOFT has a lower incidence of tricyclic-like side effects and a low incidence of nervousness, anxiety, and agitation
- The most common side effects of ZOLOFT include nausea, diarrhea or loose stools, tremor, insomnia, somnolence, and dry mouth

ZOLOFT...Once-Daily Dosing May Enhance Patient Compliance

- ZOLOFT is available in 50-mg and 100-mg scored tablets for flexible, once-daily dosing
- ZOLOFT can be taken in the morning or evening, with or without food

*Relapsing patients were those who became ill (CGI-Severity score ≥4 at any visit) during the double-blind continuation phase and who remained ill during the rest of their time in the study.

Responders in an 8-wk, open-label, acute-treatment study entered a double-blind continuation phase and were randomized to ZOLOFT or placebo. ZOLOFT daily dosage range: 50-200 mg.

References: 1. Reimherr FW, Chouinard G, Cohn CK, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. *J Clin Psychiatry* 1990;51(12, suppl B):18-27. **2.** Data on file. Pfizer Inc, New York, NY. **3.** Doogan DP, Caillard V. Sertraline in the prevention of depression. *Br J Psychiatry* 1992;160:217-222.

Please see brief summary of prescribing information on adjacent page.

ONCE-A-DAY

Zoloft™

(sertraline HCl) 50 mg, 100 mg scored tablets

BRIEF SUMMARY

ZOLOFT™ (sertraline HCl)

INDICATIONS AND USAGE: ZOLOFT (sertraline hydrochloride) is indicated for the treatment of depression.

CONTRAINDICATIONS: None known. **WARNINGS: In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that ZOLOFT (sertraline hydrochloride) not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI. PRECAUTIONS** ***General:*** **Activation of Mania/Hypomania** - During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT (sertraline hydrochloride) treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants. **Weight Loss** - Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but an overall average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss. **Seizure** - ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. Accordingly, like other antidepressants, ZOLOFT should be introduced with care in epileptic patients. **Suicide** - The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Weak Uricosuric Effect** - ZOLOFT is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown, and there have been no reports of acute renal failure with ZOLOFT. **Use in Patients with Concomitant Illness** - Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses. ZOLOFT has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received ZOLOFT in double-blind trials were evaluated and the data indicate that ZOLOFT is not associated with the development of significant ECG abnormalities. ZOLOFT is extensively metabolized by the liver. The pharmacokinetics of ZOLOFT have not been studied in patients with significant hepatic dysfunction nor have patients with significant hepatic dysfunction been evaluated during treatment with ZOLOFT. Accordingly, ZOLOFT should be used with caution in such patients. Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until the pharmacokinetics of ZOLOFT have been studied in patients with renal impairment and until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with ZOLOFT, it should be used with caution in such patients. **Interference with Cognitive and Motor Performance** - In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. ***Information for Patients:*** Physicians are advised to discuss the following issues with patients for whom they prescribe ZOLOFT: Patients should be told that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol in depressed patients is not advised. Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast-feeding an infant. ***Laboratory Tests:*** None. ***Drug Interactions:*** **Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins** - Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT (sertraline hydrochloride) to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound ZOLOFT by other tightly bound drugs. In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either ZOLOFT (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for ZOLOFT compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the ZOLOFT group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped. **CNS Active Drugs** - In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in T_{max} for desmethyldiazepam in the ZOLOFT group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown. In a placebo-controlled trial in normal volunteers, the administration of two doses of ZOLOFT did not significantly alter steady-state lithium levels or the renal clearance of lithium. Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose. The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZOLOFT and such drugs is required. **Hypoglycemic Drugs** - In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. ZOLOFT administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown. **Atenolol** - ZOLOFT (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol. **Microsomal Enzyme Induction** - Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In clinical studies ZOLOFT was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism. **Electroconvulsive Therapy** - There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT. **Alcohol** - Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol in depressed patients is not recommended. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg in mice (10 times on a mg/kg basis and the same on a mg/m² basis as the maximum recommended human dose) and at doses up to 40 mg/kg in rats (10 times on a mg/kg basis and 2 times on a mg/m² basis, the maximum recommended human dose). There was a dose-related increase in the incidence of liver adenomas in male mice receiving sertraline at 10-40 mg/kg. No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg; this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg compared to placebo controls, this effect was not clearly drug related. Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes. A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (20 times the maximum human dose on a mg/kg basis and 4 times on a mg/m² basis). ***Pregnancy — Pregnancy Category B: Teratogenic Effects*** - Reproduction studies have been performed in rats and rabbits at doses up to approximately 20 times and 10 times the maximum daily human mg/kg dose (4 to 4.5 times the mg/m² dose), respectively. There was no evidence of teratogenicity at any dose level. At doses approximately 2.5-10 times the maximum daily human mg/kg dose, sertraline was associated with delayed ossification in fetuses, probably secondary to effects on the dams. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Non-teratogenic Effects** - There was also decreased neonatal survival following maternal administration of sertraline at doses as low as approximately 5 times the maximum human mg/kg dose. The decrease in pup survival was shown to be most probably due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown. **Labor and Delivery** - The effect of ZOLOFT on labor and delivery in humans is unknown. **Nursing Mothers** - It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman. **Pediatric Use** - Safety and effectiveness in children have not been established. **Geriatric Use** - Several hundred elderly patients have participated in clinical studies with ZOLOFT. The pattern of adverse reactions in the elderly was similar to that in younger patients. **ADVERSE REACTIONS** ***Commonly Observed:*** The most commonly observed adverse events associated with the use of ZOLOFT (sertraline hydrochloride) and not seen at an equivalent incidence among placebo-treated patients were: gastrointestinal complaints, including nausea, diarrhea/loose stools and dyspepsia; tremor; dizziness; insomnia; somnolence; increased sweating; dry mouth; and male sexual dysfunction (primarily ejaculatory delay). ***Associated with Discontinuation of Treatment:*** Fifteen percent of 2710 subjects who received ZOLOFT in premarketing multiple dose clinical trials discontinued treatment due to an adverse event. The more common events (reported by at least 1% of subjects) associated with discontinuation included agitation, insomnia, male sexual dysfunction (primarily ejaculatory delay), somnolence, dizziness, headache, tremor, anorexia, diarrhea/loose stools, nausea, and fatigue. ***Incidence in Controlled Clinical Trials:*** The table that follows enumerates adverse events that occurred at a frequency of 1% or more among ZOLOFT patients who participated in controlled trials comparing titrated ZOLOFT with placebo. Most patients received doses of 50 to 200 mg per day.

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials*

Adverse Experience	ZOLOFT (N=861) (Percent of Patients Reporting)	Placebo (N=853) (Percent of Patients Reporting)
Autonomic Nervous System Disorders		
Mouth Dry	16.3	9.3
Sweating Increased	8.4	2.9
Cardiovascular		
Palpitations	3.5	1.6
Chest Pain	1.0	1.6
Central and Peripheral Nervous System Disorders		
Headache	20.3	19.0
Dizziness	11.7	6.7
Tremor	10.7	2.7
Paresthesia	2.0	1.8
Hypoesthesia	1.7	0.6
Twitching	1.4	0.1
Hypertonia	1.3	0.4
Disorders of Skin and Appendages		
Rash	2.1	1.5
Gastrointestinal Disorders		
Nausea	26.1	11.8
Diarrhea/Loose Stools	17.7	9.3
Constipation	8.4	6.3
Dyspepsia	6.0	2.8
Vomiting	3.8	1.8
Flatulence	3.3	2.5
Anorexia	2.8	1.6
Abdominal Pain	2.4	2.2
Appetite Increased	1.3	0.9
General		
Fatigue	10.6	8.1
Hot Flushes	2.2	0.5
Fever	1.6	0.6
Back Pain	1.5	0.9
Metabolic and Nutritional Disorders		
Thirst	1.4	0.9
Musculoskeletal System Disorders		
Myalgia	1.7	1.5
Psychiatric Disorders		
Insomnia	16.4	8.8
Sexual Dysfunction-Male (1)	15.5	2.2
Somnolence	13.4	5.9
Agitation	5.6	4.0
Nervousness	3.4	1.9
Anxiety	2.6	1.3
Yawning	1.9	0.2
Sexual Dysfunction-Female (2)	1.7	0.2
Concentration Impaired	1.3	0.5
Reproductive		
Menstrual Disorder (2)	1.0	0.5
Respiratory System Disorders		
Rhinitis	2.0	1.5
Pharyngitis	1.2	0.9
Special Senses		
Vision Abnormal	4.2	2.1
Tinnitus	1.4	1.1
Taste Perversion	1.2	0.7
Urinary System Disorders		
Micturition Frequency	2.0	1.2
Micturition Disorder	1.4	0.5

*Events reported by at least 1% of patients treated with ZOLOFT are included.
(1) - % based on male patients only: 271 ZOLOFT (primarily ejaculatory delay) and 271 placebo patients.
(2) - % based on female patients only: 590 ZOLOFT and 582 placebo patients.

Other Events Observed During the Premarketing Evaluation of ZOLOFT (sertraline hydrochloride): During its premarketing assessment, multiple doses of ZOLOFT were administered to approximately 2700 subjects. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section. **Autonomic Nervous System Disorders—***Infrequent:* flushing, mydriasis, increased saliva, cold clammy skin; *Rare:* pallor. **Cardiovascular—***Infrequent:* postural dizziness, hypertension, hypotension, postural hypotension, edema, dependent edema, periorbital edema, peripheral edema, peripheral ischemia, syncope, tachycardia; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, varicose veins. **Central and Peripheral Nervous System Disorders—***Frequent:* confusion; *Infrequent:* ataxia, abnormal coordination, abnormal gait, hyperesthesia, hyperkinesia, hypokinesia, migraine, nystagmus, vertigo; *Rare:* local anesthesia, coma, convulsions, dyskinesia, dysphonia, hyporeflexia, hypotonia, ptosis. **Disorders of Skin and Appendages—***Infrequent:* acne, alopecia, pruritus, erythematous rash, maculopapular rash, dry skin; *Rare:* bullous eruption, dermatitis, erythema multiforme, abnormal hair texture, hypertrichosis, photosensitivity reaction, follicular rash, skin discoloration, abnormal skin odor, urticaria. **Endocrine Disorders—***Rare:* exophthalmos, gynecomastia. **Gastrointestinal Disorders—***Infrequent:* dysphagia, eructation; *Rare:* diverticulitis, fecal incontinence, gastritis, gastroenteritis, glossitis, gum hyperplasia, hemorrhoids, hiccup, melena, hemorrhagic peptic ulcer, proctitis, stomatitis, ulcerative stomatitis, tenesmus, tongue edema, tongue ulceration. **General—***Frequent:* asthenia; *Infrequent:* malaise, generalized edema, rigors, weight decrease, weight increase; *Rare:* enlarged abdomen, halitosis, otitis media, ophthous stomatitis. **Hematopoietic and Lymphatic—***Infrequent:* lymphadenopathy, purpura; *Rare:* anemia, anterior chamber eye hemorrhage. **Metabolic and Nutritional Disorders—***Rare:* dehydration, hypercholesterolemia, hypoglycemia. **Musculoskeletal System Disorders—***Infrequent:* arthralgia, arthrosis, dystonia, muscle cramps, muscle weakness; *Rare:* hernia. **Psychiatric Disorders—***Infrequent:* abnormal dreams, aggressive reaction, amnesia, apathy, delusion, depersonalization, depression, aggravated depression, emotional lability, euphoria, hallucination, neurosis, paranoid reaction, suicide ideation and attempt, teeth-grinding, abnormal thinking; *Rare:* hysteria, somnambulism, withdrawal syndrome. **Reproductive—***Infrequent:* dysmenorrhea (2), intermenstrual bleeding (2); *Rare:* amenorrhea (2), balanoposthitis (1), breast enlargement (2), female breast pain (2), leukorrhea (2), menorrhagia (2), atrophic vaginitis (2).

(1) - % based on male subjects only: 1005; (2) - % based on female subjects only: 1705.

Respiratory System Disorders—*Infrequent:* bronchospasm, coughing, dyspnea, epistaxis; *Rare:* bradypnea, hyperventilation, sinusitis, stridor. **Special Senses—***Infrequent:* abnormal accommodation, conjunctivitis, diplopia, earache, eye pain, xerophthalmia; *Rare:* abnormal lacrimation, photophobia, visual field defect. **Urinary System Disorders—***Infrequent:* dysuria, face edema, nocturia, polyuria, urinary incontinence; *Rare:* oliguria, renal pain, urinary retention. **Laboratory Tests:** In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation. ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance. **DRUG ABUSE AND DEPENDENCE** ***Controlled Substance Class*** - ZOLOFT (sertraline hydrochloride) is not a controlled substance. ***Physical and Psychological Dependence*** - ZOLOFT has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. However, the premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. As with any new CNS active drug, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of ZOLOFT misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior). **OVERDOSAGE** ***Human Experience*** - There have been 3 cases of ZOLOFT (sertraline hydrochloride) overdosage (approximately 750-2,100 mg). No specific therapy was required for any of the 3 patients, all of whom recovered completely. ***Management of Overdoses*** - Establish and maintain an airway, insure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. There are no specific antidotes for ZOLOFT. Due to the large volume of distribution of ZOLOFT, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

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THEY WERE CAREFREE...

They were raised in a simpler time, before sugar-free and fat-free. Now hypertension, often with elevated cholesterol and blood sugar, enters the picture...

NOW THEY'RE CONCERNED...

Today's hypertensives with new concerns...

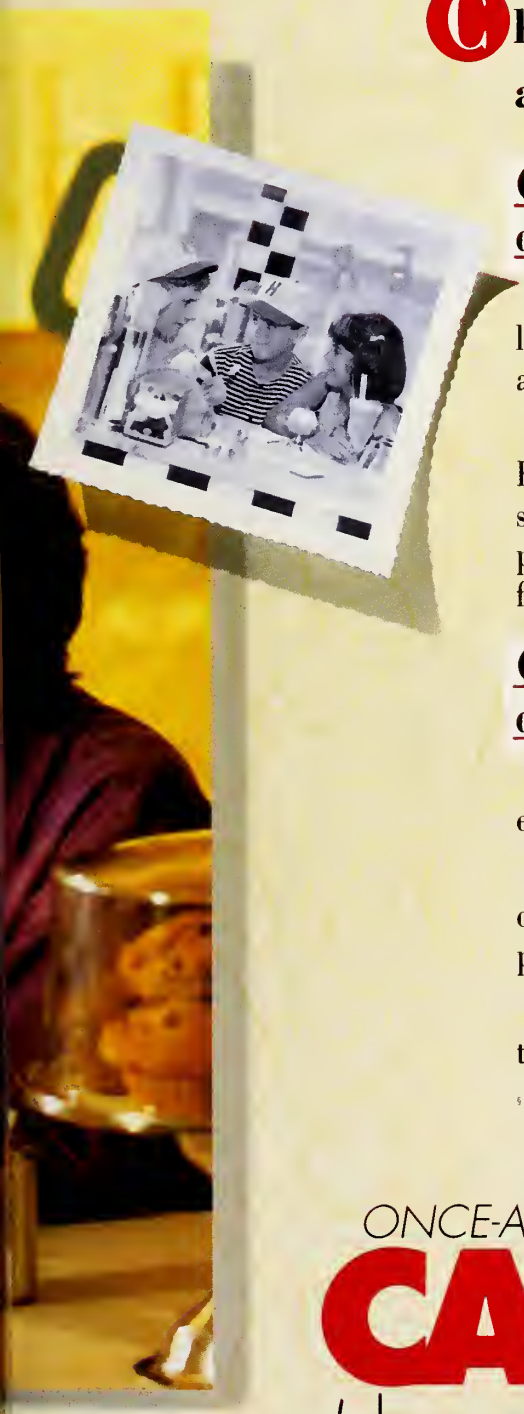
THE CARDURA

*Adapted from the interim (12 months) results of the Treatment of Mild Hypertension Study, a randomized, double-blind, placebo-controlled trial of a nutritional-hygienic regimen along with various dr therapies. All drugs (except acebutolol) were given initially in low doses. If the patient showed a diastolic blood pressure more than 95 mm Hg on three successive follow-up visits, the dosage was doubled. If blood pressure remained elevated, a second drug (chlorthalidone, except for chlorthalidone group, which was given enalapril) was added. Mean diastolic blood pressure was lowered ir various drug groups with median dosages, as follows: doxazosin (2 mg/day), 12.0 mm Hg; enalapril (5 mg/day), 12.2 mm Hg; chlorthalidone (15 mg/day), 13 1 mm Hg; and acebutolol (400 mg/day 13.7 mm Hg (n=847; $P<0.01$ vs placebo).

†n=128; $P<0.01$ vs placebo. In a pooled analysis of placebo-controlled studies with about 300 predominantly normocholesterolemic patients per treatment group, CARDURA produced a small decre in total cholesterol (-2.7%) and LDL cholesterol (-4.3%) and a small increase in the HDL/total cholesterol ratio (+4.3%).

‡Adapted from Lehtonen et al[2] (n=77; after 26 weeks: $P<0.001$ compared with week 0 for blood pressure and insulin, $P<0.05$ compared with week 0 for glucose).

GENERATION



Choose CARDURA: first-line therapy for a new generation of hypertensives.

Choose CARDURA for blood pressure control that doesn't jeopardize blood lipids.

In the Treatment of Mild Hypertension Study, CARDURA lowered diastolic blood pressure (mean 12.0 mm Hg) as effectively as enalapril, chlorthalidone, and acebutolol[1*]

CARDURA lowered blood pressure with a small increase in the HDL/total cholesterol ratio (+2.4%)* in the same study.[1†] The clinical significance of these changes is uncertain. Cholesterol is just one parameter to consider when selecting the best individualized therapy for a given patient

Choose CARDURA for blood pressure control that doesn't compromise blood sugar.

CARDURA controlled diastolic blood pressure without an adverse effect on glucose tolerance or insulin control[2‡]

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than placebo: dizziness, somnolence, and fatigue.[§]

Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo

§ These were generally mild and transient. Syncope has been reported, but rarely (<1%).

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

HYPERTENSION CONTROL FOR A NEW GENERATION.

Please see brief summary on last page.

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ONCE-A-DAY

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CARDURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory test Interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg: about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

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Nursing Mothers

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue / malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR:	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES:	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL:	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.:	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC:	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES:	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC:	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL:	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY:	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY:	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL:	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paronirla, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

Bottles of 100: 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66)

Recommended Storage: Store below 86°F(30°C).

CAUTION: Federal law prohibits dispensing without prescription.

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Pfizer Roerig

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References: 1. The Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423. **2.** Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. *Curr Ther Res* 1990;47:278-284

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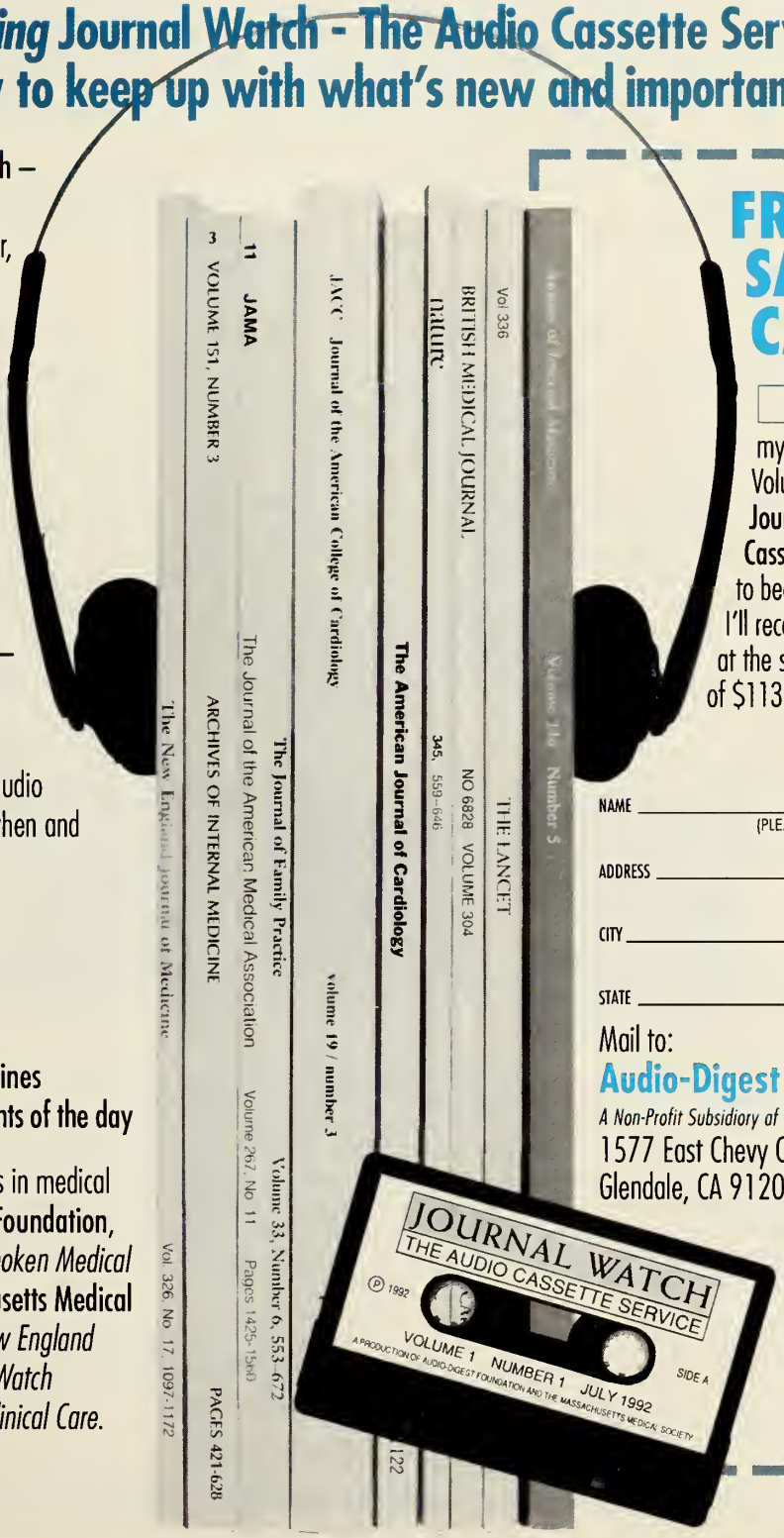

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ABSTRACTS JUNE 1992

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HEPATITIS A
PUBLIC HEALTH
HEPATITIS A ANTIBODY
COMMUNICABLE DISEASES

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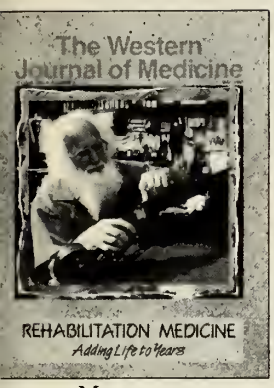

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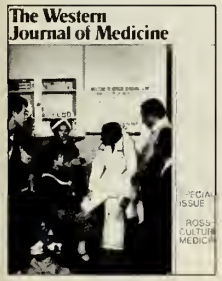

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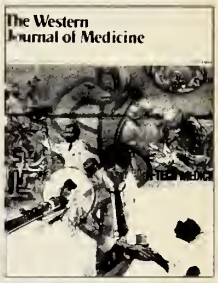

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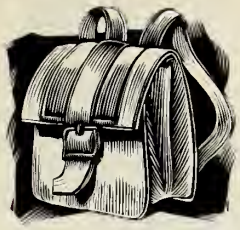

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Reversible confusional states have been observed on occasion, predominantly in severely ill patients

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However, a crossover study in healthy subjects receiving either Tagamet 300 mg q i d or 800 mg h s concomitantly with a 300 mg b i d dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older Data beyond ten days are not available (Note All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy)

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Adverse Reactions: *Diarrhea, dizziness, somnolence, headache Reversible confusional states (e g , mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported Reversible impotence in patients with pathological hypersecretory disorders receiving Tagamet, particularly in high doses for at least 12 months, has been reported The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population Gynecomastia has been reported in patients treated for one month or longer Decreased white blood cell counts in Tagamet-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported As with some other H_2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia Dose-related increases in serum transaminase have been reported Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving Tagamet has been reported Small, possibly dose-related increases in plasma creatinine have been reported Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely Rare cases of polymyositis have been reported, but no causal relationship has been established Mild rash and, very rarely, cases of severe generalized skin reactions (e g , Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists Reversible alopecia has been reported very rarely*

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1. Data from randomized, controlled studies. On file, SmithKline Beecham Pharmaceuticals.

2. Palmer RH, Frank WO, Rockhold FW, et al. Cimetidine 800 mg twice daily for healing erosions and ulcers in gastroesophageal reflux disease. *J Clin Gastroenterol.* 1990;12(suppl 2):S29-S34

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Articles

Clinical Training in Human Immunodeficiency Virus Disease for Community Physicians

The Los Angeles Experience

PETER J. KATSUFRAKIS, MD, *Los Angeles, and* STEPHEN E. RADECKI, PhD, *Long Beach, California*

In the past decade, the increased number of persons being treated for infection with the human immunodeficiency virus (HIV) has placed an enormous burden on specialty clinics. This is especially true in Los Angeles, where care of patients with the acquired immunodeficiency syndrome (AIDS) has been termed a "crisis" situation. Especially in its early stages, HIV disease can be appropriately managed by primary care physicians who provide patients with medical and psychological counseling and refer them to specialists when major AIDS-related complications develop. Physicians completing their training as recently as 5 years ago, however, received little systematic preparation in the care of HIV-infected patients and thus may lack important skills such as the ability to recognize opportunistic infections early in their course. By means of a 1-week intensive preceptorship in a high-volume AIDS clinic, we are preparing community physicians to assume a more active role in providing care for this growing patient population. In the preceptorship, participants receive one-on-one training from specialists in infectious diseases, pulmonary diseases, and hematology and oncology, as well as from internists and family physicians.

Evaluation of the clinical experience demonstrated a greater level of confidence on the part of program participants in treating HIV-infected patients and showed that participants screen and test high-risk patients in their practices and devote a substantial proportion of their practices to caring for HIV-infected patients.

(Katsufrakis PJ, Radecki SE: Clinical training in human immunodeficiency virus disease for community physicians—The Los Angeles experience. West J Med 1992 Jun; 156:619-623)

The care of persons with the acquired immunodeficiency syndrome (AIDS) in Los Angeles County presents multifaceted and growing challenges to the health care delivery system. Since 1981, more than 13,000 AIDS cases have been reported in Los Angeles County, and 4,000 patients are still alive.[1] Based on an epidemiologic projection of the AIDS epidemic in the county, the number of living patients with AIDS is expected to peak at 6,700 in 1993. By then, 31,000 additional persons in the county will be infected with the human immunodeficiency virus (HIV) for a total of 37,700 persons potentially under care,[2] or approximately 2 for each practicing physician in the county.[3]

The growth of the epidemic has strained the county's health care delivery system[4] and raised questions concerning the role of primary care physicians in providing care for this rapidly increasing patient population. Between 1984 and 1989, the percentage of primary care physicians in Los Angeles County who had evaluated a patient for AIDS or HIV infection in the preceding six months grew from 27% to almost 75%.[5] Over the same period, the proportion of primary care physicians with at least one AIDS patient in their practice grew from less than 1% to 40%.[5] A 1985 survey of county physicians' willingness to treat AIDS patients found that three fourths would refer them, and 91% believed that most community physicians are unprepared to treat AIDS patients.[6]

National surveys of primary care physicians have revealed that 68% to 77% believe that they have a responsibility to treat HIV-infected patients or have stated their willingness to provide care to these patients,[7,8] but 83% indicate that they need to know more about HIV infection.[7] Findings such as these reflect the fact that physicians completing their training as recently as five years ago received little systematic preparation in the care of HIV-infected patients. Even among third-year residents in internal and family medicine, 61% expressed concerns about the adequacy of their training in ambulatory care for patients with AIDS.[9] The most extensive experience to date in caring for these patients has been accrued by specialists and in inpatient settings. National projections analogous to the Los Angeles County data cited previously indicate a growing need for trained primary care providers to assume more of the care for HIV-infected patients—a change that has been supported by professional and government organizations.[10,11]

The care of patients with early-stage HIV infection conforms to traditional roles of primary care medicine: providing medical care, psychosocial support, and patient education. Specific components of primary HIV care include an HIV-focused history and physical examination, education concerning the natural history of the illness, and counseling regarding preventing transmission of the virus. With progression to AIDS, the patient's problems, although complex, are still manageable by primary care physicians,[12] at least between acute episodes, providing the patient with the guidance, support, and continuity required by any patient with a serious chronic illness.[13]

From the AIDS Education and Training Center for Southern California, Department of Family Medicine, University of Southern California School of Medicine, and the University of Southern California/California Medical Center Family Practice Residency, Los Angeles (Dr Katsufrakis); and the University of California Irvine/Long Beach Memorial Medical Center Family Practice Residency, Long Beach, California (Dr Radecki).

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

Of course, not all primary care physicians have the full range of clinical skills necessary to care for HIV-infected patients. Additional training and clinical experience are required, and hospitals and medical centers must recognize the importance of primary care.[12-14] One study has shown that greater experience caring for at least some of the complications of HIV infection leads to improved patient survival.[15]

Traditional sources of continuing medical education, such as lectures, seminars, publications, and self-testing programs, may be valuable but seldom provide the depth and clinical experience necessary to care for HIV-infected patients. Moreover, an AIDS-related continuing medical education program carried out among primary care physicians in Los Angeles County showed no effect on their competence to deal with AIDS patients, consistent with other studies that show a limited impact of traditional continuing medical education aimed at unselected audiences of physicians.[16] A survey of Los Angeles County physicians showed that either hospital inservice training or a short rotation through a university AIDS clinic is perceived as an effective means for community physicians to learn about AIDS and revealed that more than 40% of physicians would avail themselves of an AIDS clinic rotation if one were offered.[6] We describe a clinical rotation designed to provide community physicians with experience caring for patients with HIV infection or AIDS.

Clinical Training in HIV Disease for Primary Care Physicians

The clinical training program is an intensive one-week preceptorship in an ambulatory care setting developed for community physicians, physician assistants, nurse practitioners, and third-year residents. The overall goals of the program are to supply primary care providers with the knowledge and skills necessary to manage the complications of HIV infection commonly seen in an outpatient setting and to increase the number of clinicians working with HIV-infected patients in the community. The following specific goals determined the structure and content of the clinical preceptorship:

- Develop proficiency in identifying patients at risk for HIV infection.
- Increase knowledge of the symptoms and findings associated with the opportunistic complications of HIV infection.
- Enable program participants to employ essential diagnostic tests and pharmacologic therapies rationally and effectively.
- Expand the range of problems cared for by primary care providers and develop appropriate referral practices.
- Supply a strategy for maintaining proficiency in the face of rapidly changing knowledge.

The clinical training program is conducted by the AIDS Education and Training Center for Southern California, which is funded by the Health Resources and Services Administration to provide AIDS education for primary care providers in Los Angeles, Orange, Ventura, Santa Barbara, Riverside, and San Bernardino counties. The University of Southern California serves as a primary site, providing an intensive clinical preceptorship as part of its AIDS education activities. A list of similar training centers throughout the nation and the areas served by each has been published elsewhere.[17]

Most of the clinical preceptorship takes place in the multidisciplinary HIV/AIDS clinic of the Los Angeles County-University of Southern California Medical Center. The clinic, established in 1985, cares for approximately 2,500 patients needing 3,000 patient visits per month. Of these patients, 54% have an AIDS-related condition, 38% have AIDS as defined by Centers for Disease Control criteria,[18] and 8% are asymptomatic but seropositive for HIV. A recent demographic analysis showed that 25% are Hispanic, 15% are African American, 1% are Asian, and the rest are non-Hispanic white; 4% of clinic patients are women. Homosexuality or bisexuality is the major risk factor for HIV infection in 90% to 92% of patients. Clinic staff members coordinate outpatient and inpatient management of patients with AIDS and AIDS-related complex and of HIV-positive patients with mild opportunistic infections. The clinic operates morning and afternoon sessions five days a week, along with one evening session per week. In the past, the clinic used ten examining rooms, three offices, and one treatment room to provide care for a substantial portion of AIDS patients receiving care in the county. Overcrowding in the clinic resulted in a waiting period of as long as six months, prompting extensive media coverage. The overcrowding has been relieved by the construction of a three-story outpatient clinic dedicated to HIV patient care, which was completed in June 1991.

The clinic is designed so that specialists come to it rather than patients being referred to other specialty clinics. This arrangement provides an ideal setting for the week-long preceptorship, during which participants interact with specialists in infectious diseases, neurology, epidemiology, pulmonary disease, and hematology and oncology, as well as general internists and family physicians.

Specialty clinics address needs not met in the AIDS clinic, such as the evaluation of ophthalmologic or surgical problems. Mental health needs are addressed by a team of psychiatrists, psychologists, nurses, and social workers. In addition to standard examinations, special procedures performed in the clinic include venipuncture for emergency blood tests; arterial puncture for blood gas analysis; bone marrow aspiration and biopsy; lumbar puncture; thoracentesis; skin biopsy; the administration of blood transfusions, infusions, and medications; and parenteral hydration. These procedures allow for a fairly comprehensive workup and treatment in an outpatient setting, decreasing the average length of hospital stay for inpatients. The clinic is affiliated with the University of Southern California School of Medicine, which is a member of the AIDS Clinical Trials Group funded by the National Institutes of Health and a member of the California Cooperative Treatment Group for AIDS Research; this affiliation provides patients with access to numerous experimental therapies for HIV infection and its complications under investigational protocols.

The patient volume and staff expertise provide a useful setting for training primary care professionals to care for HIV-infected patients. The training program is designed for physicians who have already reached a certain level of com-

		Monday	Tuesday	Wednesday	Thursday	Friday
Morning	Activity	Orientation HIV Risk Assessment Test Counseling	Cytomegalovirus Clinic	Primary Care	Primary Care	Primary Care Mental Health
	Faculty Specialty	Family Practice	Family Practice Infectious Disease Ophthalmology	Internal Medicine Infectious Disease Neurology	Family Practice	Family Practice Psychology
	Location	Classroom	Clinic	Private Practice 1	Private Practice 2	Clinic
Afternoon	Activity	Intake Clinic	Primary Care Tuberculosis Clinic	Primary Care	Kaposi's Sarcoma Clinic	Primary Care Wrapup
	Faculty Specialty	Family Practice	Infectious Disease Pulmonology Family Practice	Internal Medicine Infectious Disease Neurology	Hematology	Family Practice
	Location	Clinic	Clinic	Private Practice 1	Clinic	Clinic

Figure 1.—The curriculum for clinical training in diagnosing and treating human immunodeficiency virus (HIV) disease is shown for a typical 1-week session.

petence with basic knowledge regarding HIV infection. Candidates are selected for this clinical preceptorship on the basis of their experience in diagnosing and managing HIV infection and also based on the proportion of minorities and medically indigent persons they serve. To be accepted for a clinical rotation, candidates must submit an application and other documentation and complete an informational form, which serves as a pretest and indicates the knowledge and experience level of the applicant. The goal in selecting trainees is to increase the number of trained providers caring for populations at risk for HIV infection, which are currently underserved. Training is available to physicians and physician assistants from the six-county service area at no cost to the trainee. Trainees from outside this area have also been accepted as space permits.

Description of the Course

The purpose of the clinical preceptorship is to enable trainees to manage common, chronic, HIV-associated conditions and to diagnose and refer life-threatening complications at an early stage in their presentation. Specific objectives of the preceptorship are that, following completion of the course, trainees will be able to

- Provide appropriate initial evaluation of HIV-infected patients and subsequent health surveillance,
- Counsel patients regarding maintaining their health and reducing the risk of transmission to others,
- Recognize and treat common minor complications of HIV infection,
- Recognize early signs and symptoms of major complications and appropriately treat patients or refer them for definitive treatment, and
- Serve as a resource to other clinicians for managing HIV-infected patients.

Trainees spend one full week in the clinical training program. Training takes place during patient visits, with emphasis on clinical instruction in the context of direct patient care. One half-day is spent in the classroom reviewing HIV-associated pathologic disease and a clinical approach to HIV-infected patients; the rest of the week is spent in direct patient care. Physician specialists model appropriate primary care and supervise the trainees' evaluation and treatment of patients. Throughout the experience, one-on-one teaching is provided by the supervising preceptor during rotations in the initial evaluation/intake clinic, primary care clinics, cytomegalovirus clinic, pulmonary clinic, Kaposi's sarcoma clinic, and in two private medical offices. Training rotations take place every week, with the exception of holiday weeks, and are available throughout the year. The schedule for a typical week is shown in Figure 1. Only two trainees are admitted for each week.

Educational experiences conducted away from the medical center include visits to two private medical offices (Figure 1) that care for HIV-infected patients, which allow trainees to compare their experiences in a county-run clinic with the level of care provided in a private office. Instruction in counseling patients before and after testing for HIV infection is also available through a state-sponsored anonymous testing site.

A comprehensive syllabus supplements clinical experiences.[19] Chapters focus on the general clinical skills necessary to evaluate HIV-infected patients as well as on specific diseases and pathologic processes, which are categorized by organ system. The syllabus also contains patient referral resources and sources for physicians to update their knowledge and maintain proficiency.

After completing the one-week course, trainees are interviewed to assess their satisfaction with the preceptorship. A follow-up assessment of trainees' knowledge and practice patterns relative to HIV-infected patients is conducted between 6 and 12 months after the completion of training.

Results of Evaluation

An assessment of trainees' experiences immediately following training indicates overwhelming satisfaction with the preceptorship. Most trainees state that their expectations have been met and that, as a result of training, they could now diagnose and treat HIV-infected patients.

A practice profile of 21 community physicians who completed clinical training during the first two years of the

course,* measured over a six-month period from June through November 1990, showed that each of these physicians identified an average of 84 patients at risk for HIV infection (9% of all patients seen) and recommended HIV testing for an average of 74 patients over six months. Of the 21 participants in the training program who were profiled, 19 (90%) provide care for HIV-positive patients at least until symptoms develop and most refer their patients to specialists only when major AIDS-related complications develop.

Program graduates reported that 5% of the patients seen over the preceding six months were HIV-positive and indicated that their level of comfort in providing counseling to HIV-positive patients had increased: "much higher" compared to pretraining level, 9 (43%); "higher," 10 (48%); "the same," 2 (9%). An equivalent change was shown for participants' level of confidence regarding the care they provide to these patients.

Ratings of the usefulness of the knowledge and skills acquired during the clinical experience showed that intake experience and primary care experiences within the AIDS clinic were rated as most useful. Specialty rotations within the AIDS clinic (cytomegalovirus clinic, pulmonary clinic, dermatology and Kaposi's sarcoma clinic) were rated highly but below the primary care experiences, whereas the private practice experiences and mental health clinic were rated as less useful. In the private practice training sites, participants noted that they experienced a reduced level of hands-on patient care compared with training received at the AIDS clinic.

Discussion

A national survey of primary care physicians' experience and opinions regarding HIV infection showed that two thirds had treated a patient with AIDS and that three fourths had treated an HIV-positive patient. Despite this, only 42% would welcome an AIDS patient into their practice, while 48% would rather refer patients with HIV infection.[7] This outlook is reinforced by a California-based study showing that most primary care physicians lack the knowledge and skills to assume responsibility for the care of patients infected with HIV.[20] The effect of these factors is to place an excessive burden of care on specialized providers[21] that could be alleviated if primary care physicians assumed greater responsibility for this care.[13]

Although this training program directly addresses the need for more skilled primary care professionals in one region, it serves as a model for other institutions to use in training the medical community to deal with the AIDS epidemic. Many aspects of the preceptorship can be adapted to other facilities training professionals to manage HIV infection.

This training program is most readily adapted to other medical centers that provide care to a large number of HIV-infected patients in an environment allowing ready access to specialists. In this setting, training could easily be provided by designating one or several physicians as educators to instruct trainees during the course of ongoing patient care. A physician and medical education specialist could support training activities by preparing supporting curricular materials. Candidates for training could initially be solicited from local medical societies, hospital staffs, or public health clinics; subsequent marketing would include physicians already serving patients known to be HIV infected or at risk (such as persons using intravenous drugs), but who need additional training and have not yet participated in a similar training program.

The educational needs of the local medical community should determine the focus of any training program. If significant numbers of persons have not yet become infected with HIV in the program's geographic area, more appropriate training would be targeted toward identifying persons at risk and counseling those persons to be tested and to avoid high-risk behaviors. Alternatively, communities where AIDS is present will have a growing need for professionals able to give effective primary care, including an awareness of diagnosis and treatment of opportunistic complications.

In areas not near a medical center that cares for a large number of HIV-infected patients, the need for trained primary care professionals is perhaps even greater. Resources for training may be limited, but a workable plan for education regarding HIV diagnosis and treatment should be feasible. Assessing community educational resources provides a starting point. Public health clinics or private physicians already serving HIV-infected patients may have experience and expertise that can be used to coordinate training of other physicians.

The AIDS epidemic represents a present and growing danger. Knowledge remains our most effective weapon to limit its effects; even if the spread of HIV were halted completely, however, the reservoir of undiagnosed infection gives every physician in the United States a high probability of treating someone infected with HIV. Well-trained physicians have the tools to fight many of the complications of this disease; untrained physicians put their patients at risk for needless morbidity and mortality. Educating primary care physicians to treat HIV-infected patients should be a cornerstone in our fight against AIDS.

*In addition to community physicians, 59 residents, 2 nurses, 13 physician assistants, 12 nurse practitioners, and 1 dentist have been trained at the AIDS Education and Training Center for Southern California. An additional 14 community physicians who completed training during the second half of 1990 are excluded from these evaluation results.

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INHERIT TENSE

Other people inherit
paid-off mortgages
and blue chip stocks,
porcelain figurines
and heirloom jewels—
family estates
valuable as fatted calves.
My ancestors left me
a deficient heart
and calcium deposits,
compounding cholesterol
and high-yield hypertension—
half-empty bottles
of nitroglycerin and Percodan.
So, I sip non-fat milk
instead of spooning
thick clots of cream,
dish up oat bran
instead of savoring
smoked duck pate,
nosh handfuls of nuts
instead of gnawing
blood red meat.
I'm banking
on my own
flesh and blood
that I'll be saved
on account
of myself.

MARAEL JOHNSON
Del Mar, California

Articles

Hepatitis A Outbreak in Anchorage, Alaska, Traced to Ice Slush Beverages

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The Alaska Department of Health and Social Services investigated a community outbreak of hepatitis A in Anchorage. A total of 57 persons who had hepatitis A between June and September 1988 were studied. Patients ranged from 1 to 54 years of age. A market was implicated as the source of the outbreak. An employee who prepared beverage mixtures in a bathroom was a contact of a person who had had hepatitis A 2 months before the outbreak; the employee was reported to have been jaundiced 3 to 4 weeks before the peak of the outbreak. The administration of immune globulin had an efficacy of 100% (95% confidence limits 69, 100%) in preventing hepatitis A among household contacts of primary cases. Similar beverages are sold by convenience markets and many other businesses nationwide. It is important to ensure that safe food-handling practices are followed by such establishments.

(Beller M: Hepatitis A outbreak in Anchorage, Alaska, traced to ice slush beverages. West J Med 1992 Jun; 156:624-627)

In July 1988, the Alaska Department of Health and Social Services (ADHSS) investigated a hepatitis A outbreak in Peters Creek, a suburban area of Anchorage with approximately 4,000 residents. Hepatitis A is a reportable condition in Alaska, and surveillance for communicable diseases is conducted by ADHSS. From 1972 to 1985, an average of slightly less than one hepatitis A infection per week was reported in Anchorage.[1] If the incidence in Peters Creek was the same as that in the city as a whole, less than one case per year of hepatitis A would be expected.

Patients and Methods

Persons with hepatitis A were initially identified through passive reporting of confirmed and possible infections by health care professionals to ADHSS. As soon as the outbreak was recognized, a physician assistant in Peters Creek and several physicians with nearby offices were contacted and requested to report any patient(s) with hepatitis-like symptoms. There was extensive local media coverage of the outbreak, and ADHSS sent letters to all physicians in Anchorage requesting that any patient with possible hepatitis A be reported.

A primary case was defined as any instance where a Peters Creek resident or visitor had the onset of serologically confirmed hepatitis A (or, for someone living with such a person, clinical hepatitis) between June 14 and July 21, 1988. Serologic confirmation required the presence of immunoglobulin (Ig) M hepatitis A antibody (anti-HA) in serum. Clinical hepatitis was defined as either the presence of jaundice or a serum aminotransferase level of at least 2.5 times the upper limit of normal.

A secondary case was defined as any instance where a person had either serologic or clinical hepatitis A with onset of the disease 20 to 50 days after exposure to a primary case. A tertiary case was defined as any instance where a person had either serologic or clinical hepatitis A with onset of the disease 20 to 50 days after exposure to a secondary case.

Serologic testing for IgM anti-HA and total anti-HA was done by private laboratories or the Alaska State Public Health Laboratory using commercial enzyme immunoassay kits. Family members of infected patients were given standard doses (0.02 to 0.04 ml per kg of body weight) of commercially obtained immune globulin by their health care providers or the Anchorage Department of Health and Human Services (HHS).

A case-control study to examine possible causes of the outbreak was conducted by comparing primary cases with family members who were either asymptomatic or seronegative for total anti-HA or IgM anti-HA. The first 14 people with reported cases and all 22 of their household contacts were interviewed by a public health nurse or physician and questioned extensively about social events, restaurant meals, grocery shopping, travel, and other community activities. Although they were not included in the case-control study, the 18 remaining people with primary cases, as well as those with secondary and tertiary cases, were also interviewed.

The efficacy of immune globulin in preventing secondary infection was calculated using the following formula:

$$\text{Efficacy} = (1 - \text{OR}) \times 100\%$$

where OR is the odds ratio.[2] The odds ratio was calculated from the number of secondary cases among household contacts who had and had not received immune globulin. Confidence limits were calculated using the exact method.[3]

Environmental Investigation

Public and private water supplies in Peters Creek were tested for total and fecal coliform levels by HHS and the Alaska Department of Environmental Conservation. A mar-

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ABBREVIATIONS USED IN TEXT

ADHSS = Alaska Department of Health and Social Services
anti-HA = hepatitis A antibody
CL = confidence limits
HHS = Anchorage Department of Health and Human Services
Ig = immunoglobulin
OR = odds ratio

ket implicated as the source of the outbreak was inspected by HHS, and ADHSS conducted an investigation of its employees.

Results

A total of 32 primary, 23 secondary, and 2 tertiary cases were reported in this outbreak (Figure 1). Of these, 53 patients were IgM anti-HA–positive; the other 4 patients did not have serologic testing but met the clinical case definition. Overall, the median age of patients was 18.0 years (range 1 to 54 years), and 31 (54%) were female. Information regarding symptoms was not systematically collected; however, of 37 patients for whom complete information was available, 29 (78%) had jaundice, 11 (30%) had vomiting, and 11 (30%) had fever or chills (Table 1). Three persons were briefly admitted to hospital; there were no deaths.

Among the 23 secondary cases, 14 persons (61%) were household members of people with primary cases, 7 (30%) were visitors to primary-case households, and 2 (9%) were infected by a person with a primary case who was a cook at a social event. Both people with tertiary infection resided with people who had secondary infection. The median age of secondary and tertiary cases was 25.0 years, older than that of primary cases, which was 13.0 years (Wilcoxon rank sum $P = .042$).

Case-Control Study

No common social events, restaurants, or community activities were identified. The 14 persons classified as primary cases, however, had consumed at least one ice slush beverage purchased from a Peters Creek convenience market (market A) between May 23 and June 10, 1988. This interval was identified because few persons were able to recall the specific day on which they had consumed an ice slush beverage. Of the 22 asymptomatic or anti-HA–negative household members (controls), 7 had consumed an ice slush beverage during this interval. The association between the consumption of an ice slush beverage purchased from market A and infection with hepatitis A was significant (OR = ∞; 95% confidence limits [CL] 4.9, ∞). All 18 patients with primary

TABLE 1.—*Symptoms of Hepatitis A in 37 Persons, Anchorage, Alaska, 1988*

Symptom	Persons With Symptom No.	(%)
Jaundice	29	(78)
Fever or chills	11	(30)
Vomiting	11	(30)
Abdominal pain	7	(19)
Diarrhea	4	(11)
Anorexia	4	(11)
None	1	(3)

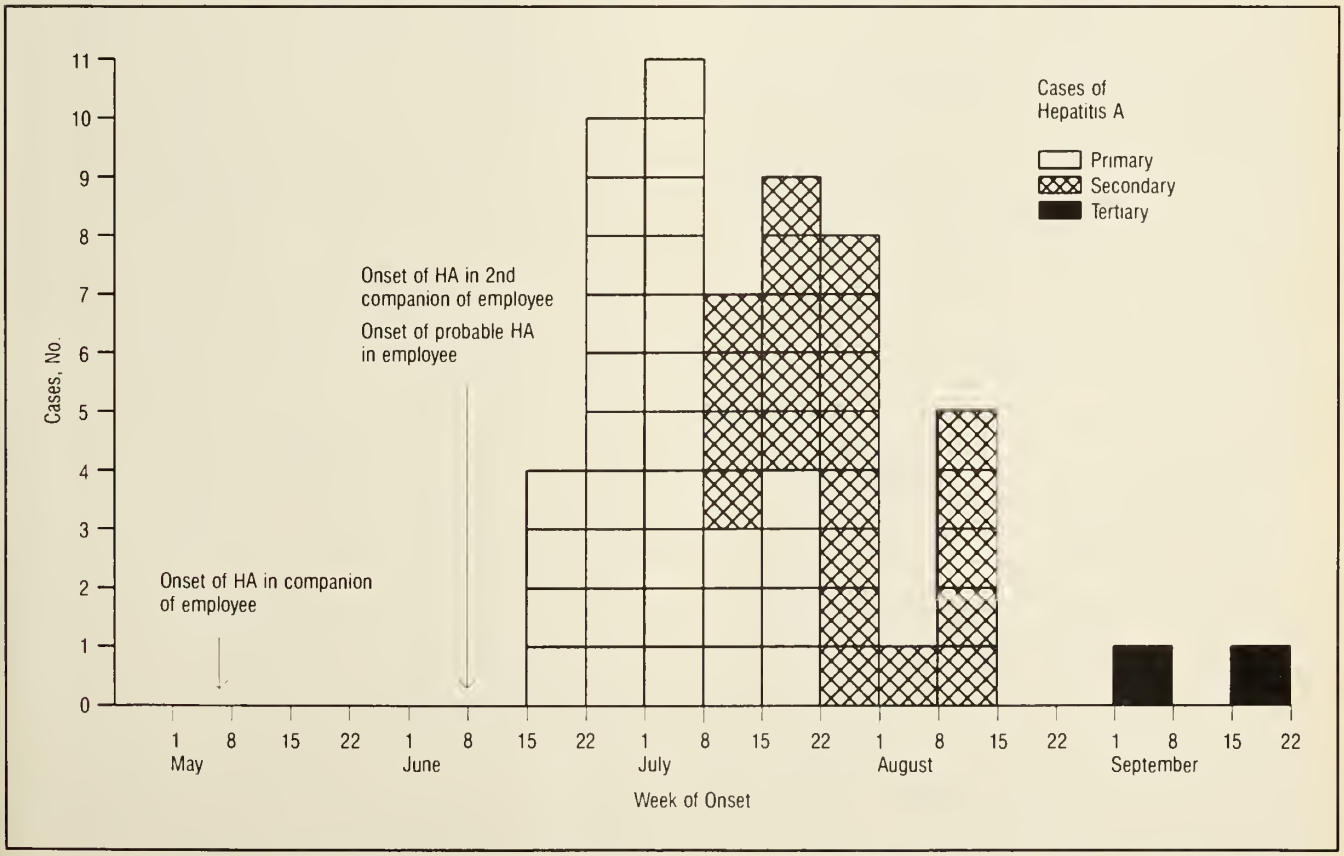

Figure 1.—Reported cases of hepatitis A (HA) are depicted by week of onset for the outbreak in Peters Creek, Alaska, from May to September 1988.

infection not included in the case-control study also had had this exposure.

Efficacy of Immune Globulin Prophylaxis

The 32 persons with primary infection had 64 household contacts who were initially asymptomatic. Among these persons, 14 secondary cases resulted, for a secondary attack rate of 22%. Information on immune globulin administration was available for 52 (81%) of the household contacts. These contacts resided in households in which either *all* contacts were given immune globulin (n = 8) or *none* were given immune globulin (n = 9). Of 22 contacts who received immune globulin within two weeks of diagnosis of the primary case in their household, none subsequently became ill, compared with 13 secondary cases among the 30 contacts who were not treated (efficacy = 100%, 95% CL 69, 100%).

Among the 12 household contacts with unknown immune globulin status, 1 secondary case was identified. Assuming that this person had received immune globulin and the 11 other contacts had not, the immune globulin efficacy is 90% (95% CL 23, 100%).

The median age of the contacts who received immune globulin (23.5 years) was not significantly different from that of contacts who did not (22.0 years; Wilcoxon rank sum $P = .32$).

Environmental Investigation

Water samples were collected from market A, a community well serving at least 60 homes in Peters Creek, a private well that supplied water to several case households, and taps from four individual case households. All samples had total and fecal coliform counts in the acceptable range for safe drinking water and consistent with uncontaminated water supplies.

Two employees of market A were responsible for preparing a mixture used to fill a freezer that dispensed ice slush beverages. They prepared the mixture by adding approximately 630 ml of a commercial liquid concentrate (containing sugar, flavoring, and other ingredients) to an empty 1-gallon (3.79-liter) bottle. The bottle was then filled with water from a bathroom sink and kept in a refrigerator until needed. Mixing utensils were stored next to a toilet in a back room of the market. From one to six bottles of mixture were prepared daily.

Beverages were dispensed from the freezer to customers. Employees had no contact either with the mixture when the freezer was filled or with ice slush when beverages were dispensed. The freezer was not regularly cleaned, and the market did not keep cleaning or maintenance records.

In mid-July, four of the five employees of market A underwent serologic testing for hepatitis A. All four were IgM anti-HA–negative. The fifth employee, one of the two persons who prepared beverage mixture, refused to be tested. This employee had two companions who had had laboratory-confirmed hepatitis A during the two months before the outbreak. The first was a 23-year-old woman with illness onset on May 5 (Figure 1). The other, her 21-year-old sister, became jaundiced on June 8. These three people had been together during the week of May 5, and although the employee denied illness, one of his companions said he was jaundiced during the first week of June.

On July 14, HHS ordered the market to stop selling all ice slush beverages. Conditions under which sales could resume, the most important being acceptable beverage preparation procedures, were specified by HHS. The market elected to permanently discontinue selling ice slush beverages.

Discussion

This investigation implicated ice slush beverages sold by a convenience market as the vehicle for a hepatitis A outbreak. Both the case-control study and the inspection and investigation at market A supported this conclusion. Because the peak of the outbreak occurred approximately 60 days after an employee who prepared the beverage mixture had had exposure to hepatitis A (and, according to a companion of the employee, approximately 30 days after the employee was jaundiced), it is likely that the employee was the source of the outbreak.

Although one published hepatitis A outbreak investigation reported a household secondary attack rate of 0%,[4] most outbreaks have secondary attack rates of between 5% and 12%.[5-10] Selection bias may have contributed to the relatively high rate observed here (22%) because primary cases may have been more completely ascertained in households with secondary transmission; several persons with primary infection and with mild or moderate symptoms were identified only after medical care was sought for secondarily infected household members.

The analysis of immune globulin efficacy is reassuring even though the data, like those from most field investigations, are incomplete. Among household contacts who were given immune globulin within two weeks of diagnosis of the primary case, there were no secondary cases. This observation, coupled with the occurrence of 13 secondary cases among 30 household members who were not given immune globulin, strongly supports the use of immune globulin as currently recommended.[11] Because household contacts were not consistently tested for anti-HA, some may have been immune. All household contacts of each person with primary infection either received or did not receive immune globulin; thus, it was not possible to distinguish between the effectiveness of immune globulin and a possible household effect. Because Peters Creek is a relatively homogeneous community in which most households are of similar size and socioeconomic status, it is unlikely that the observed effectiveness of immune globulin was due to household differences in immunity, cleanliness, food handling, or other factors.

This outbreak points out the importance of proper food-handling practices. Common-source hepatitis A outbreaks are uncommon in the United States: In 1987, there were 25,280 reported cases of hepatitis A, but only 9 confirmed food-borne hepatitis A outbreaks (involving 187 persons) reported to the US Centers for Disease Control.[12,13] If food handlers adhered to recommended food handling and hygienic practices, these outbreaks might be prevented. The procedures used by the market to prepare the beverage mixture were clearly unacceptable. The ice slush beverage implicated in this outbreak, and other beverages requiring mixing, are often sold by convenience markets, gasoline stations, movie theaters, and other establishments; this investigation highlights the potential for the transmission of hepatitis A and other enteric diseases at such businesses. If employees follow proper food-handling techniques and observe good personal hygiene practices, especially hand washing, the risk of disease transmission can be substantially reduced.

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TWELVE WORDS

I even dream of calling you,
to discuss my options, as it were,

to ask if the pain in the shoulder
is related to the mass in the neck

which seems less swollen, even though
it occurred just after the drugs

which may have caused the nausea
and certainly precipitated the weight loss,

(not that I had any leeway),
unlike the hair loss, which I agree

is merely vanity in a man my age,
but it focused on the tracheostomy

which I press with my thumb to speak, but,
I'm never understood, and yet,

only you come by and talk to me
without shouting as others do,

suggesting that I am also deaf,
(which I am certainly not),

so that I must respond by writing
on this yellow pad in bold script

knowing that your time is valuable
needing to see many people,

so I have promised to limit myself
to twelve words each day.

MARC J. STRAUS, MD©
Chappaqua, New York

TWELVE MORE WORDS

I even celebrated your speechless valor,
drill sergeant for 20 years,

screaming with fine-tuned cords,
"eyes forward, chin up, follow orders,"

which you never did, drinking
gallons of beer, smoking ceaselessly,

until those cords were cut out,
already covered with cancer cells,

finding their way relentlessly around
until you were 104 pounds

of quiet fire, reduced to writing notes
on a little yellow pad with a cheap pencil

without ever complaining about the nausea,
the mouth sores, the hair loss,

because we had a pact,
when the mass was gone,

a pact I commemorated in a poem
called *Twelve Words*—that you

wouldn't wait 3 days until
your kidneys stopped, your gut bled,

your lungs filled with fluid, so
I have only 12 more words:

Austin, you son of a bitch,
did you have to die today!

MARC J. STRAUS, MD©
Chappaqua, New York

Articles

Adolescent Health Care in a Large Multispecialty Prepaid Group Practice

Who Provides It and How Well Are They Doing?

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Adolescents are at risk for pregnancy, sexually transmitted diseases, suicide, homicide, accidents, and substance abuse. Adolescent medicine involves an overlap of many skills needed to provide routine medical care, as well as care for those conditions that require psychosocial assessment. We report the results of a mail survey covering care of this age group by practitioners of pediatrics, internal medicine, obstetrics and gynecology, family practice, and adolescent medicine in a large, multispecialty, prepaid group practice.

The mail survey covered 10 areas of adolescent care. Adolescent medicine physicians expressed the highest level of perceived knowledge and competence in these areas, with family practitioners ranked second. More than 50% of internists and pediatricians felt only fair to poor competence for a variety of adolescent conditions, whereas a third of internists and pediatricians reported that they liked to care for adolescents. Physicians in all 4 of the primary care specialties reported a need for a teen health center for both consultation and education. These results are similar to those reported for pediatricians and primary care physicians in private practice and for residents in internal medicine.

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The Task Force on Pediatric Education[1] concluded in 1978 that evidence suggests that "major health deficits exist among the over 40 million Americans between the ages of 10 and 21." Adolescents are still at notable risk for pregnancy, sexually transmitted diseases, suicide, homicide, accidents, and substance abuse.[2] Are physicians adequately trained to address these problems?

Providing care to adolescents often requires a diversity of skills and knowledge about general medical care, infectious diseases, sexually transmitted diseases, gynecology, and psychosocial assessment. The challenge is to organize and effectively deliver an unusual collection of services, particularly those related to sexuality and reproduction, violent behavior, and emotional and mental health, as well as those included in routine health care.

In evaluating medical school graduates between 1975 and 1977, the Task Force on Pediatric Education found that almost 60% of the graduates rated their training in adolescent health care as insufficient. A 1986 study of practicing pediatricians in Los Angeles County reported that more than 60% of participants rated their competence and previous training as low in relation to the pelvic examination, the sexually active teen, and adolescent psychological issues.[3] In a 1990 study of pediatricians in New York State, Marks and colleagues reported that fewer than half the respondents provided anticipatory guidance regarding sexuality, and only 14% questioned teens about depression.[4] They concluded that most of the surveyed pediatricians were inadequate in meeting the health needs of adolescents. Blum and Bearinger found that primary care—internal medicine, family practice, pediatrics—physician respondents in a national survey reported self-perceived limitations in the areas of eating disorders, learning disabilities, chronic illness, and delinquent behavior.[5] Slap reported that pediatric residents felt underskilled in many areas of adolescent health care.[6] Comerci and co-workers in a 1988 survey of pediatric program directors found that more time is being spent in training on adolescent health issues since 1978.[7] Chastain and associates reported no higher self-perceived skills among pediatricians trained after 1976 than between 1966 and 1975, however.[8]

Although the deficiencies listed here are well documented, no adequate evaluation has been conducted of primary care and adolescent medicine physicians in a health maintenance organization (HMO) where continuing medical education is readily available. We present the results of a survey that was sent to all primary care and adolescent medicine physicians of the Southern California Permanente Medical Group. This group of physicians provides care for about 300,000 adolescents in the HMO, representing 15% of the total plan enrollment.

Methods

We developed a survey using the format of a previous questionnaire assessing self-perceived skills and comfort of physicians in areas of adolescent health care.[3] The questions were in three general categories: demographics of the physi-

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TABLE 1.—*Physicians' Attitudes Toward and Time Spent in Caring for Adolescents*

Practice Characteristics and Time Spent Caring for Adolescents, %	Specialty: Internal Medicine, n=170	Family Practice, n=129	Pediatrics, n=137	Obstetrics and Gynecology, n=81	Adolescent Medicine, n=14	P Value*
Current practice time for adolescents	6.8	11.7	13.8	17.8	82.1	<.001
Desired practice time for adolescents	12.0	19.0	15.2	21.9	89.4	<.001
Physicians who like working with adolescents	34.1	61.2	31.4	50.6	100.0	<.001

*Multigroup comparison where at least 1 comparison is significantly different at $P < .001$.

cian respondents; the perceived technical competency, level of comfort, and practice style of the physicians when dealing with adolescent patients; and the role of a teen health center in Kaiser Permanente. Physicians were asked to record most of their responses on a 1 to 4 Likert scale—excellent, good, fair, poor. Some questions were multiple choice with an option for additional comments. For this survey, adolescents were defined as persons between the ages of 13 and 22. The teen health center consists of a multidisciplinary team of professionals including adolescent medicine physicians and obstetrician-gynecologists, a health educator, psychiatric social worker, and a center coordinator, all with special training and competence in adolescent medicine, providing medical and psychosocial care in a preventive manner.

Questionnaires were distributed to all full-time and part-time physicians in five specialties: internal medicine, family practice, pediatrics, obstetrics and gynecology, and adolescent medicine. The questionnaires were mailed in two waves, the first in October 1988 and the second in November 1988 to nonrespondents to the first wave. A cover letter from the principal investigators described the purpose of the study. Participation and disclosure of the physicians' names and specialties were voluntary. The study was approved by the Southern California Kaiser Permanente Institutional Review Board.

The statistical analysis was done using the SAS statistical program. Descriptive and correlational analyses, with appropriate tests of significance—multigroup χ^2 and analysis of variance methods—were used to generate results.*

*Girma Wolde-Tsadik, PhD, Senior Statistician, Southern California Kaiser Permanente, statistically reviewed this study.

Results

Of the 1,138 surveys mailed, 603 (53%) were returned; response rates were similar across specialties. The respondents had a mean age of 43 years, and 24% were women. There were no statistically significant differences between respondents and nonrespondents with respect to age, sex, or years in practice. The average number of years in practice was 14, with a range of 1 year to more than 40 years. It should be noted that adolescent medicine, obstetrics and gynecology, and family practice physicians care for teenagers between the ages of 13 and 22, pediatricians treat children up to age 18, and internists care for teenagers older than 18 years. Therefore, the responses by specialty correspond to caring for adolescents in these age groups.

Table 1 summarizes the results of the questions asked of physicians regarding the amount of practice time devoted to caring for adolescents. There is a fairly narrow range—12% to 22%—for the time physicians other than adolescent medicine physicians reported they would like to spend with adolescents.

When asked whether they liked working with adolescents, only a third of internists and pediatricians responded affirmatively. More than half of family practitioners, half of obstetricians and gynecologists, and all adolescent medicine physicians liked working with adolescents.

Physicians were asked about their medical knowledge and technical competence for "routine medical care" and in these ten areas of adolescent care: adolescent development, sports injury and evaluation, genitourinary care, pregnancy-related care, birth control, sexually transmitted diseases, eating and weight control problems, sexuality, psychological

TABLE 2.—*Physicians Reporting Poor to Fair Medical Knowledge and Competence, %**

Type of Adolescent Health Care	Specialty: Internal Medicine, n=173	Family Practice, n=129	Pediatrics, n=137	Obstetrics and Gynecology, n=79	Adolescent Medicine, n=14	Total, n=535	P Value†
Routine medical care	15	3	5	67	0	17	<.001
Adolescent development	69	20	15	83	0	43	<.001
Sports evaluation or injury	81	24	51	93	14	59	<.001
Genitourinary care	32	5	44	3	0	23	<.001
Pregnancy-related care	74	31	68	0	7	49	<.001
Birth control	55	5	65	0	0	36	<.001
Sexually transmitted diseases	26	3	52	0	0	23	<.001
Sexuality	65	32	60	18	0	47	<.001
Eating and weight problems	76	56	71	80	21	69	<.001
Psychological problems	62	34	56	78	0	54	<.001
Drug problems	64	43	63	74	7	59	<.001
Average for all items except "routine medical care"	60	26	50	55	6	--	<.001

*Poor to fair values are combined.
†Multigroup comparison where at least 1 comparison is significantly different at $P < .001$.

problems, and drug abuse and dependency. Table 2 shows the statistically significant differences between the specialties in perceived level of knowledge and technical competence for each of these areas.

Most internists rated themselves as having poor or fair knowledge and technical competence to deal with eight of ten adolescent care problems. The only areas of perceived competence for most of the internists were caring for genitourinary problems and sexually transmitted diseases. Most family practitioners surveyed rated themselves as good to excellent in knowledge and competence in all areas except eating and weight problems.

TABLE 3.—*Treatment and Referral Patterns by Specialty in 10 Adolescent Care Areas*

Specialty	Evaluate and Treat, %	Refer if Complicated, %	Refer All Patients, %	P Value*
Internal medicine	28	52	20	<.001
Family practice	54	40	6	<.001
Pediatrics	32	47	21	<.001
Obstetrics and gynecology	34	36	30	<.001
Adolescent medicine	75	24	1	<.001

*Multigroup comparison where at least 1 comparison is significantly different at $P < .001$.

Of the 137 pediatricians surveyed, 68 (50%) rated themselves as having poor or fair knowledge and technical competence with eight of ten teen health problems. Like internists, they rated themselves as good to excellent in genitourinary care. Pediatricians, however, rated themselves as good to excellent more often than internists in dealing with adolescent development (85% versus 31%).

The responses of specialists in obstetrics and gynecology refer only to female adolescent patients. Of these specialists, 55% rated themselves as poor to fair in knowledge and technical competence with six of ten adolescent health care problems. Their areas of greatest competence were birth control (100%), sexually transmitted diseases (100%), pregnancy-related care (100%), genitourinary care (98%), and sexuality (82%). They also were the only specialty to express inadequate knowledge in routine medical care.

None of the adolescent medicine specialists thought themselves incompetent in providing most services to adolescents. Although their competence was perceived to be higher than other specialties, two areas where some respondents rated themselves as poor to fair were eating and weight problems (21%) and sports injury and evaluation (14%). Eating and weight problems was an area that received a low rating from all specialties. Only adolescent medicine physicians felt competent in caring for psychological and drug-related problems.

The physicians were also asked how they would handle problems in each of the ten adolescent care areas. The choices were to evaluate and treat all patients, refer if care is complicated, or refer all patients. Table 3 outlines the results by specialty. Table 4 details the results of the "refer all patients" category for each of the ten areas by specialty.

There are certain limitations to our study. The level of knowledge and technical competence was based on self-perception, which may not reflect actual knowledge and competence. The response rate was only slightly more than 50%, but this rate is comparable to other reported surveys.

Discussion

Our survey examines the views by specialty of physicians who care for adolescents in an HMO. The results are consistent with others that report that pediatricians, primary care physicians, and internal medicine and pediatric residents in non-HMO settings feel their knowledge and technical competence for treating adolescents are less than desirable.[2-6] This study also compares the perceptions of four primary care specialties with those of adolescent medicine. The perceived knowledge and competence in caring for most adolescent health problems was significantly lower for the four specialties in comparison to the adolescent medicine physicians.

Examining the survey results by specialty contradicts some common beliefs. Pediatricians are often designated as the group that is trained and appropriate to care for adolescents. The American Academy of Pediatrics stressed this opinion in its 1978 Task Force on Pediatric Education.[1] Only a third of the pediatricians in our survey liked working with adolescents, however, compared, for example, with more

TABLE 4.—*Physicians Referring All Adolescent Patients, %*

Health Care Area	Specialty: Internal Medicine, n=170	Family Practice, n=130	Pediatrics, n=136	Obstetrics and Gynecology, n=79	Adolescent Medicine, n=14	Total, n=529	P Value*
Routine medical care	2	0	0	28	0	5	<.001
Adolescent development	15	2	3	41	0	12	<.001
Sports evaluation or injury	17	1	4	59	0	15	<.001
Genitourinary care	8	0	13	1	0	6	<.001
Pregnancy-related care	54	25	59	0	8	38	<.001
Birth control	27	2	48	0	0	21	<.001
Sexually transmitted diseases	4	0	21	1	0	7	<.001
Sexuality	24	6	25	9	0	17	<.001
Eating and weight problems	33	20	34	48	0	31	<.001
Psychological problems	15	4	16	39	0	16	<.001
Drug problems	29	12	35	53	0	29	<.001
Average for all items except "routine medical care"	20	6	21	30	1	--	<.001

*Multigroup comparison where at least 1 comparison is significantly different at $P < .001$.

than half of family practice physicians. Pediatricians were also equal to internists in listing the greatest number of areas where they considered themselves only poorly or fairly competent to treat adolescents.

A possible explanation for the lower proportion of pediatricians who liked working with adolescents and their lower perceived knowledge and competence is the relatively small portion of their practice (14%) devoted to these patients. Because most see younger patients—86% of their patients are younger than 13 years—it is not unexpected that they would feel least comfortable and competent with adolescent health care.

Internists often perceive themselves as responsible for the care of young adults. A 1989 position paper by the American College of Physicians discussed the importance of adolescent health care.[9] In our survey, internists were equal to pediatricians both in their low level of liking to work with adolescents and in the large number of areas where they ranked themselves poorly or fairly knowledgeable and competent. Internists do not treat many adolescents—6% of their practice. When they do see adolescents, they feel least knowledgeable and comfortable with sports evaluation and injury, eating and weight problems, pregnancy, and adolescent development, followed closely by sexuality and drug and psychological problems. Few of these areas are stressed in internal medicine training. Although it is not surprising that many internists would refer all patients for pregnancy-related care (like the other nonobstetric specialties), it was notable that a third would refer all cases of eating and weight problems in this age group.

Family practitioners treat the greatest number of adolescents in the United States.[10] Aside from specialists in adolescent medicine, this was the group that rated themselves the most knowledgeable and competent in the various areas of adolescent health care. They spent about 12% of their practice time with adolescents. Many felt least comfortable and competent with regular genitourinary care, eating and weight problems, and drug problems. Whereas family practice physicians were least likely to refer these patients, these three areas were where consultation would be sought.

Although patients may perceive specialists in obstetrics and gynecology to be the physicians who provide primary care for women of all ages, these physicians generally provide specialty care. This was confirmed by their high level of self-perceived competence in areas such as contraception and pregnancy-related care but less competence in routine medical care, adolescent development, drug problems, and psychological problems. Of the obstetrician-gynecologists responding, 28% would prefer to refer patients for all routine medical care, and 41.5% would refer all nonobstetric adolescent care problems.

In contrast to the other specialties, adolescent medicine physicians spend the most time (82%) providing care to adolescents. Although they are more comfortable than physicians in the other specialties surveyed in dealing with adolescents, they felt least competent and comfortable with eating and weight problems, sports evaluation and injury, pregnancy, and drug problems.

There are several possible reasons why many physicians do not feel informed and technically competent about certain adolescent care areas:

- Without adequate education, training, and practice, physicians may not be comfortable discussing issues such as sexually transmitted diseases, pregnancy decisions, birth control, sexuality, eating disorders, depression, stress, problems at home and school, or substance abuse with adolescent patients and their families. Specific skills are required to establish the rapport necessary with adolescents to broach these sensitive subjects and to obtain accurate information.
- Most physicians focus on organic disease as the sole cause for the health complaints of teenagers. The medical care of adolescents requires physicians to approach problems in a biobehavioral way that requires a knowledge of adolescent development and an awareness of psychosocial and physical factors in the causes of disease. Most medical training is based on an approach that emphasizes a single, linear cause and effect. It is therefore understandable that these physicians will have the greatest resistance for the integrated systems view so important in understanding adolescent problems.
- There is a lack of adolescent medicine education during undergraduate training because this material is not mandatory in medical schools. This deficiency in the curriculum may be due to the recent emergence of adolescent medicine as a recognized specialty and a lack of adolescent medicine specialists in medical schools and community practice. Further, there are few postgraduate education programs in adolescent medicine available across the country.
- The relatively small proportion of adolescents in primary care physicians' practices may result in a lack of sufficient discomfort in handling adolescent patients' problems to motivate them to seek additional education and training.
- In this practice setting, the proportion of practice the primary care physicians devoted to adolescents and the amount of time they wished to see adolescents followed closely in parallel. The proposed use of a teen health center as a resource for consultation and education and, to a more limited degree, primary care for adolescents is logical given the organizational structure and perceived need for additional education (Table 5).

TABLE 5.—*Physicians Who Would Use a Teen Health Center, %*

	Specialty						
Reason for Use	*Internal Medicine, n=163*	*Family Practice, n=126*	*Pediatrics, n=135*	*Obstetrics and Gynecology, n=79*	*Adolescent Medicine, n=12*	*Total, n=515*	*P Value**
Consultation	67	66	74	68	42	68	0.164
Primary care	35	13	44	48	42	34	<.001
Education	55	71	52	68	33	60	<.001
Not used at all	8	17	5	1	8	8	<.001

*Multigroup comparison where at least 1 comparison is significantly different at $P < .001$.

Recommendations

The following recommendations for improving the health care of adolescents are appropriate for physicians across specialties and practice settings:

- Improve the competency of practicing physicians by increasing postgraduate continuing medical education in adolescent care. Of all physicians in this study, 45% were interested in additional training and education to better treat adolescents. Physicians in all specialties devote many hours annually to continuing medical education to meet licensure and specialty certification requirements and to upgrade their skills. There should be ample opportunity to improve their knowledge and competency in caring for adolescents through continuing education options.
- Improve the competency of new medical school graduates by including mandatory adolescent medicine education as part of undergraduate and residency programs.
- Increase the availability of adolescent medicine specialists to primary care physicians for consultation and referral through resources such as teen centers in managed care programs, universities, and hospitals. More than 93% of physicians in our study said they would use a resource such as a teen health center in some way, and 68% said they would use it for consultation.

The combination of better physician education and adolescent medicine specialists provides a foundation on which to build educational, consultation, and referral programs that can meet the expressed needs of physicians in a number of specialties to better treat adolescent patients.

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Conferences and Reviews

Drug Dosing Guidelines in Patients With Renal Failure

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The metabolism and excretion of many drugs and their pharmacologically active metabolites depend on normal renal function. Accumulation and toxicity can develop rapidly if dosages are not adjusted in patients with impaired renal function. In addition, many drugs that are not dependent on the kidneys for elimination may exert untoward effects in the uremic milieu of advanced renal disease. A familiarity with basic pharmacologic principles and a systematic approach are necessary when adjusting drug dosages in patients with abnormal kidney function. The distinct steps involve calculating the patient's glomerular filtration rate, choosing and administering a loading dose, determining a maintenance dose, and a decision regarding monitoring of drug concentrations. If done properly, therapy in renal patients should achieve the desired pharmacologic effects while avoiding drug toxicity. Physicians must not oversimplify the pharmacologic complexities presented by patients with renal failure by relying excessively on nomograms and "cookbook" equations. In addition to a reduced glomerular filtration rate, patients with renal disease often have alterations in pharmacokinetics such as bioavailability, protein binding, hepatic biotransformation, and volume of distribution. An awareness of biologically active or toxic metabolites of parent compounds that accumulate when the glomerular filtration rate is reduced is also necessary to avoid toxicity. The effects of dialysis on drug elimination and the need for supplemental dosing are additional considerations in patients undergoing renal replacement therapy.

(Swan SK, Bennett WM: Drug dosing guidelines in patients with renal failure. West J Med 1992 Jun; 156:633-638)

Drug elimination by the kidneys correlates with the glomerular filtration rate. It is thus logical to use this measurement for adjusting dosages in patients with renal failure. Other pharmacokinetic variables, however, may be altered in patients with renal insufficiency, including drug absorption, volume of distribution, degree of protein binding, and biotransformation. Hence, dosage adjustments cannot be based solely on decreased renal excretory rates.

Absorption rates of many therapeutic agents may be reduced by azotemia-associated vomiting or sluggish gut motility due to uremic neuropathy, the use of phosphate binders, or both. Aluminum-containing binders may form insoluble compounds with certain drugs such as tetracycline or ferrous sulfate and block absorption. Bowel wall edema in a patient with hypoalbuminemia may also diminish drug absorption.

The volume of distribution for a specific drug is derived by dividing the total amount of drug in the body by its plasma concentration. It does not refer to a specific anatomic compartment per se; instead, it is used mathematically to determine the dose of a drug necessary to achieve a desired plasma concentration. The volume of distribution for a specific drug may be altered in patients with uremia, specifically by alterations in the extracellular fluid volume state. For example, volume contraction tends to decrease and edema and ascites increase the volume of distribution for hydrophilic and highly protein-bound agents. Conversely, digoxin, methotrexate, and insulin have decreased distribution volumes in the uremic state. As a general rule, plasma concentrations of a drug correlate inversely with its volume of distribution.

Protein binding is often altered in the uremic state and can affect the volume of distribution and the proportion of free or biologically active drug available. Specifically, protein binding of acidic drugs (Table 1) is diminished in uremic patients due to a displacement by organic acid accumulation and structural alterations in albumin. For example, penicillins and phenytoin, which are normally highly protein-bound, are displaced from albumin by organic acids that accumulate in patients with uremia, leading to increased levels of free or "active" drug. Conversely, higher concentrations of unbound drug are available for enzymatic metabolism in the liver, which may lead to increased drug clearance rates, particularly if drug metabolites are excreted by nonrenal routes.

TABLE 1.—*Acidic Compounds With Decreased Protein Binding in Uremio*

Barbiturates	Phenytoin
Cephalosporins	Salicylate
Clofibrate	Sulfonamide
Diazoxide	Valproate
Furosemide	Warfarin
Penicillins	

Biotransformation may also be altered by renal insufficiency. Hepatic oxidative pathways for certain drugs (phenytoin, propranolol) may be accelerated, and other metabolic functions such as acetylation, hydrolysis, and reduction may be slowed. Active or toxic metabolites of parent compounds may accumulate in patients with renal failure. The antiarrhythmic agent procainamide is metabolized to *N*-acetyl-procainamide, which is excreted by the kidneys. Thus, the antiarrhythmic properties and toxicity of procainamide and its active metabolite are additive, especially in patients with renal failure. A commonly used narcotic, meperidine, is biotransformed to normeperidine, which undergoes renal excretion. Although this metabolite has little narcotic effect, it lowers the seizure threshold as it accumulates in uremic pa-

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tients. Similarly, active metabolites of benzodiazepines can accumulate in patients with impaired renal function, resulting in prolonged sedation.

Thus, pharmacologic considerations in patients with renal impairment demand an appreciation of altered pharmacokinetic principles in this patient population. Detailed pharmacokinetic information with extensive reference material is beyond the scope of this discussion and can be found elsewhere.

Dosimetry in Renal Failure

The following outline provides a stepwise approach to assist physicians in prescribing drug therapy for patients with renal failure. Again, it must be emphasized that these steps simply provide a framework for dosage adjustments in patients with renal impairment and must be modified on a case-by-case basis.

Initial Assessment

A history and physical examination constitute the first step in assessing dosimetry in patients with renal impairment. Specifically, renal dysfunction should be defined as acute or chronic and the cause ascertained if possible. In addition, a history of previous drug intolerance or toxicity should be determined. The patient's current medication list (both prescription and nonprescription formulations) must likewise be examined to identify possible adverse drug interactions and nephrotoxins. The physical examination will provide height and body weight information that may be necessary, for example, in an obese patient to calculate ideal body weight. For men, the ideal body weight is 50 kg plus 2.3 kg for each 2.5 cm over 152 cm. For women, the formulation is 45.5 kg plus 2.3 kg per 2.5 cm over 152 cm. An assessment of the extracellular fluid volume is also key because alterations in this measurement can affect the distribution volumes of many pharmacologic agents. The identification of extrarenal disease—hepatic dysfunction—may lead to the need for even greater dosage adjustments, depending on the pharmacologic agents administered.

Calculate Creatinine Clearance

The rate of drug elimination by the kidneys is proportional to the glomerular filtration rate. It is important to remember that serum creatinine and blood urea nitrogen levels are crude and often inaccurate measures of renal function. Thus, creatinine clearance (C_{cr}) is more accurately used to approximate the glomerular filtration rate. Because body mass and age affect serum creatinine concentrations and clearance, C_{cr} can be estimated by the Cockcroft and Gault equation[1]:

$$C_{cr} = \frac{(140 - \text{age})(\text{body weight in kg})}{72 \times \text{serum creatinine}}$$

In women, this result should be multiplied by 0.85. Remember that this equation represents only an approximation of the glomerular filtration rate even if accurately done. Specifically, the serum creatinine level does not reflect the C_{cr} in patients with rapidly changing renal function. In acute renal dysfunction, timed urine collections should be done and mid-collection serum creatinine values used to calculate the C_{cr}. Both the calculated and endogenous forms of C_{cr} overestimate the inulin clearance, the conventional "gold standard" in glomerular filtration determination.[2] Nevertheless, the C_{cr} is an approximation useful in clinical dosimetry.

Choose a Loading Dose

In many cases, a rapid achievement of therapeutic drug concentrations is the pharmacologic goal. If several doses of a drug are administered at uniform intervals, steady-state drug concentrations are achieved after 3.3 drug-elimination half-lives. Because the half-life may be greatly prolonged in renal failure, effective therapy may be greatly delayed if maintenance doses are adjusted to reflect the renal failure elimination half-life. Thus, a standard loading dose, practically speaking, should be administered to patients with renal failure to reach therapeutic drug levels rapidly. The loading dose can be calculated by the following formula where *Vd* is the volume of distribution (liters per kg), IBW is the ideal body weight (kg), and *Cp* is the desired plasma concentration (mg per liter):

$$\text{Loading dose} = Vd \times \text{IBW} \times Cp$$

As discussed previously, if extracellular volume depletion exists, the volume of distribution may be reduced for certain pharmacologic agents, and slight reductions in the loading dose would be prudent. Specifically, drugs with narrow therapeutic:toxic profiles such as digoxin and ototoxic aminoglycosides should be administered with a 25% reduction in their loading dose when volume contraction is present.

Choose a Maintenance Dose

Deriving a maintenance dose for a drug ensures steady-state blood concentrations and diminishes the likelihood of subtherapeutic regimens or toxicity. If the clinical need for drug action is not urgent, maintenance doses can be used from the initiation of therapy to gradually achieve steady-state concentrations without the need for a loading dose. Adjustments in maintenance doses for patients with renal insufficiency can be accomplished by one of two methods or a combination of the two. The "interval extension" method involves lengthening the time period between individual doses of a drug that corresponds to the degree of delayed drug excretion and reflects the extent of renal impairment. This method is particularly useful for drugs with a wide therapeutic range and long half-life. It can, however, result in periods of subtherapeutic drug levels between doses and should be used judiciously. Another alternative, the "dosage reduction" method, involves reducing the absolute amount of drug administered at each dosing interval proportional to the patient's degree of renal failure. The dosing interval remains unchanged in this setting, and more constant drug concentrations are generally achieved. It risks greater toxicity, however, because the difference between peak and trough levels is minimized and trough levels tend to be higher. Thus, combining these two approaches often becomes necessary to provide effective therapy for patients with renal dysfunction while minimizing toxicity. Recommendations for maintenance dosage adjustments have been published elsewhere,[3] and a limited number of clinically relevant examples are tabulated in Table 2. Again, these recommendations provide only a general guideline for dosing adjustments and must be adapted to a specific patient's situation.

Monitoring Drug Levels

Varying the dose or dosing interval for a given therapeutic agent may not be sufficient to guarantee therapeutic efficacy and avoid toxicity in patients with renal failure. If a prescrib-

TABLE 2.—*Dosage Adjustments for Patients With Renal Failure*

Drug, Toxicity, and Notes	*Elimination and Metabolism*	*Half-life (Normal/ESRD), hours*	*Plasma Protein Binding, %*	*Volume of Distribution, liters/kg*	*Method**	*Adjustment for Renal Failure GFR, ml/min* 10-50	< 10	*Supplement for Dialysis*
ANTIMICROBIAL AGENTS								
Aminoglycoside Antibiotics *Ototoxic, nephrotoxic; rare respiratory paralysis; serum levels to ensure efficacy. Postthemodialysis dose is ⅔ of normal maintenance dose or ½ of a loading dose; 50% to 90% absorbed from peritoneum; volume of distribution larger with obesity, edema, or ascites*								
Gentamicin sulfate	Renal	1.7-2/20-60	<5	0.23-0.26	D, I	30-70 every 12	20-30 every 24-48	Yes (He, PD)
Concurrent use of penicillins may result in subtherapeutic blood levels								
Netilmicin sulfate	Renal	2.2-2.7/35-72	<5	0.16-0.30	D, I	20-60 every 12	10-20 every 24-48	Yes (He, PD)
Tobramycin	Renal	2.5/27-60	<5	0.22-0.33	D, I	30-70 every 12	20-30 every 24-48	Yes (He, PD)
Concurrent use of penicillins may result in subtherapeutic blood levels								
Cephalosporin Antibiotics *Rare allergic interstitial nephritis; absorbed well when administered intraperitoneally, may cause bleeding in patients with renal failure*								
Cefamandole nafate	Renal	1/6-11	75	0.16-0.25	I	6-8	12	Yes (He, PD)
Cefazolin sodium	Renal	1.8-2/40-70	80	0.13-0.22	I	12	24-48	Yes (He, PD)
Cefadizime	Renal	2.5-4/7.4	80-90	0.13-0.2	D	50-100	50	No (He, PD)
Cefoxitin sodium	Renal	1/13-23	41-75	0.13-0.39	I	8-12	24-48	Yes (He, PD) No (PD)
May raise creatinine levels by interfering with assay								
Ceftazidime	Renal	1.2/13-25	17	0.28-0.4	I	24-48	48-72	Yes (He, PD)
Ceftriaxone sodium	Renal (hepatic)	7-9/12-24	85-95	0.12-0.14	I	Unchanged	24	No (He, PD)
Monitor levels in dialysis patients								
Cefuroxime	Renal	1.1-1.4/17	33	0.13-1.8	I	8-12	24	Yes (He)
Cephalothin sodium	Renal	0.5-1/3-18	65	0.26	I	6-8	12	Yes (He)
Miscellaneous Antibacterial Antibiotics								
Aztreonam	Renal	1.7-2.9/6-8	50-60	0.1-0.2	D	50-75	25	Yes (He, PD)
Chloramphenicol	Hepatic	1.6-3.3/3.7	60	0.6-1.0	--	Unchanged	Unchanged	No (He, PD)
t-½ Markedly prolonged with combined liver and kidney dysfunction								
Ciprofloxacin	Hepatic	3-6/6-9	20-40	2.1	D	50	33	Yes (He, PD)
Poorly absorbed with the use of antacids or phosphate binders								
Clindamycin HCl	Hepatic	2-4/3-5	60-95	0.6-1.2	--	Unchanged	Unchanged	No (He, PD)
Erythromycin	Hepatic	1.4/5-6	60-95	0.8	D	Unchanged	50-75	No (He, PD)
Ototoxic in high doses in patients with ESRD								
Fleroxacin	Renal (hepatic)	9-12/17-25	<30	>1.5	D	50-100	50	No (He, PD)
Imipenem	Renal	1/4	13-21	0.30	D	50	25	Yes (He)
Lomefloxacin HCl	Renal	7-8/38-44	15	2.2-2.5	D	50-100	50	No (He, PD)
Metronidazole	Hepatic	6-14/21	20	0.25-0.85	D	Unchanged	50	Yes (He)
Norfloxacin	Hepatic	3.5-6.5/8	14	<0.5	I	12-24	Avoid	No (He)
Spectinomycin HCl	Renal	1.6/16-29	5-20	0.25	--	Unchanged	Unchanged	No (He, PD)
Sulfadiazine	Renal	8-17	22-34/30-55	?	D I	25-50 8-24	Avoid 48-72	?
Sulfamethoxazole	Renal	9-11/20-50	40-60	0.28-0.38	I	18	24	Yes (He)
Trimethoprim	Renal	9-13/20-49	30-70	1-2.2	I	18	24	Yes (He)
Has antifolate activity								
Vancomycin HCl	Renal	6-8/200-250	10-50	0.47-0.84	I	72-240	240	No (He, PD)
Ototoxic at serum levels > 50 mg/ml, 40% to 70% absorbed from peritoneum								

(Continued on next page)

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Drug, Toxicity, and Notes	Elimination and Metabolism	Half-life (Normal/ ESRD), hours	Plasma Protein Binding, %	Volume of Distribution, liters/kg	Method*	Adjustment for Renal Failure GFR, ml/min 10-50	< 10	Supplement for Dialysis
Penicillins *Agents in this group cause allergic interstitial nephritis; seizures and coagulopathy occur at high blood levels*								
Amoxicillin	Renal	0.9-2.3/5-20	15-25	0.26	I	6-12	12-16	Yes (He)
Ampicillin *Contains 3 mEq Na^+/gram*	Renal	0.8-1.5/7-20	8-20	0.17-0.31	I	6-12	12-16	Yes (He) No (PD)
Dicloxacillin sodium	Renal	0.7/1-2	91-98	0.13-0.19	--	Unchanged	Unchanged	No (He, PD)
Mezlocillin sodium *Contains 1.9 mEq Na^+/gram*	Renal	0.6-1.2/2.6-5.4	20-46	0.17-0.20	I	6-8	8	No (He, PD)
Nafcillin sodium *Causes coagulopathy*	Hepatic	0.5/1.2	80-90	0.31-0.38	--	Unchanged	Unchanged	No (He, PD)
Penicillin G *Potassium salt has 1.7 mEq/million units; causes convulsions, false-positive urine protein reactions*	Renal	0.5/6-20	40-60	0.3-0.42	D	75	25-50	Yes (He)
Piperacillin sodium *Contains 1.9 mEq Na^+/gram*	Renal	0.8-1.5/3.3-5.1	20-40	0.18-0.30	I	6-8	8	Yes (He)
Ticarcillin disodium *Contains 5.2 mEq Na^+/gram*	Renal	1.2/16	45-60	0.14-0.21	D, I	1-2 grams every 8 h	1 gram every 12 h	Yes (He) No (PD)
Tetracycline Antibiotics *Agents in this group potentiate acidosis, raise blood urea nitrogen and phosphorus levels, and increase catabolism; their use should be avoided in renal failure*								
Doxycycline *Group drug of choice for extrorenal infection*	Hepatic	15-24/18-25	80-93	0.75	--	Unchanged	Unchanged	No (He, PD)
Antifungal Antibiotics								
Amphotericin B *Nephrotoxic; causes renal tubular acidosis, hypokalemia, and nephrogenic diabetes insipidus*	Nonrenal	24/24	90	4	I	24	24-36	No (He, PD)
Fluconazole *May increase blood cyclosporine levels*	Renal	22-36/98	11	0.5-0.6	I	24-48	48-72	Yes (He)
Flucytosine *Causes hepatic dysfunction and marrow suppression is more common in azotemic patients*	Renal	3-6/75-200	<10	0.6	I	12-24	24-48	Yes (He, PD)
Ketoconazole	Hepatic	1.5-3.3/3.3	99	1.9-3.6	--	Unchanged	Unchanged	No (He, PD)
Antimycobacterial Antibiotics								
Clofazimine	Nonrenal	70 d/70 d	Low	High	--	Unchanged	Unchanged	No (He, PD)
Ethambutol HCl *Causes decreased vision acuity and peripheral neuritis*	Renal	4/7-15	10-30	1.6-2.3	I	24-36	48	Yes (He)
Isoniazid	Hepatic	0.7-4/8-17	<10	0.6	D	Unchanged	50	Yes (He)
Pyrazinamide	Hepatic	9.5/9.5	50	0.7	D	Unchanged	Avoid	Avoid
Rifampin *May cause acute renal failure, potassium wasting, and renal tubular defects; biologically active metabolite, desacetyl-rifampicin*	Hepatic	1.5-5/1.8-11	60-90	0.9	--	Unchanged	Unchanged	No (He)
Antiviral Antibiotics								
Acyclovir *Neurotoxic in patients with renal failure; may cause acute renal failure if rapidly administered intravenously*	Hepatic (renal)	2.1-3.8/20	15-30	0.6-0.8	D, I	5 mg/kg every 12-24 h	2.5 mg/kg every 24 h	Yes (He)
Amantadine HCl	Renal	12/500	60	4-5	I	48-72	168	No (He, PD)
2′,3′-Dideoxycytidine (ddC)	Renal	0.5-2.2/Prolonged	?	0.54-0.6	D	50-75	25-50	?
2′,3′-Dideoxyinosine (ddI)	Hepatic (renal)	0.5-4.64/Prolonged	<5	1	D	75-100	50-75	?
Foscarnet sodium	Renal	36-72/Prolonged	?	1-1.7	D	15-50	Avoid	Yes (He)
ANTIHYPERTENSIVE AGENTS *In this group, blood pressure is best guide to dose and interval*								

Adrenergic Modulators								
Clonidine *Rebound hypertension occurs if drug is abruptly withdrawn; tricyclic antidepressants decrease efficacy; potentiates central nervous system depressant effects of alcohol, sedatives*	Hepatic (renal)	6-23/39-42	20-40	3-6	--	Unchanged	Unchanged	No (He, PD)
Methyldopa *Causes orthostatic hypotension; retroperitoneal fibrosis; prolonged hypotension due to retained active metabolites; interferes with serum creatinine measurement*	Renal (hepatic)	1.5-6/6-16	<15	0.5	I	8-12	12-24	Yes (He)
Prazosin HCl *Profound hypotension may occur with first dose*	Hepatic	2-3/2-3	97	1.2-1.7	--	Unchanged	Unchanged	No (He, PD)
Angiotensin-converting Enzyme Inhibitors *Hypotensive effect magnified by natriuretic agents or sodium depletion; hyperkalemia; acute renal dysfunction with bilateral or transplant renal artery stenosis; dry cough occurs in 5% to 10% of patients*								
Benazepril HCl	Renal (hepatic)	21-22/Prolonged	>95	0.09-0.16	D	25-100	25-50	No (He)
Captopril *Causes rare proteinuria, nephrotic syndrome; dysgeusia, granulocytopenia; can increase serum digoxin levels*	Renal (hepatic)	1.9/21-32	25-30	0.7-3	D, I	75 every 12-18 h	50 every 24 h	Yes (He)
Cilazapril	Renal (hepatic)	7.5/8.2	?	0.29-0.36	D	25-100	25-50	Yes (He)
Enalapril maleate *Enalaprilat is the active moiety formed in liver*	Renal (hepatic)	11-24/40-60	50-60	?	D	75-100	50	Yes (He)
Lisinopril	Renal	12.6/40-50	<10	1.3-1.5	D	50-75	25-50	Yes (He)
β-Blockers								
Atenolol *Significant accumulation in patients with ESRD*	Renal	6-9/15-35	<5	1.1	D, I	50 every 48 h	50 every 96 h	Yes (He)
Betaxolol HCl	Hepatic	14-22/31.2	55	4.9-9.8	D	Unchanged	50	No (He, PD)
Labetalol HCl	Hepatic	3-8/3-8	50	5.6	--	Unchanged	Unchanged	No (He, PD)
Metoprolol tartrate	Hepatic	2.5-4.5/2.5-4.5	8	5-6	--	Unchanged	Unchanged	Yes (He)
Propranolol HCl *Metabolites may accumulate; increases bilirubin level by assay interference; less frequent doses in some patients with ESRD; hypoglycemia reported in ESRD*	Hepatic	2-6/1-6	90-96	3-4	--	Unchanged	Unchanged	No (He)
Calcium Blocking Agents *Headache, flushing, and dizziness in patients with renal disease; may increase serum digoxin and cyclosporine levels*								
Diltiazem HCl *Active metabolites; acute renal dysfunction reported*	Hepatic	2-8/3.5	98	3-5	--	Unchanged	Unchanged	No (He, PD)
Isradipine	Hepatic	1.9-4.8/10	?	3-4	--	Unchanged	Unchanged	No (He, PD)
Nifedipine *Active metabolites; edema; acute renal dysfunction reported*	Hepatic	4-5.5/5-7	92-98	1.4	--	Unchanged	Unchanged	No (He, PD)
Nisoldipine	Hepatic	6.6-8/6.8-10	99	2.3-7.1	--	Unchanged	Unchanged	No (He, PD)
Verapamil HCl *Active metabolites; acute renal dysfunction reported*	Hepatic	3-7/2.4-4	83-93	3-6	--	Unchanged	Unchanged	No (He, PD)
Cardiac Glycosides *Add to uremic gastrointestinal symptoms; serum levels guide therapy; toxicity enhanced by dialysis potassium and magnesium removal*								
Digitoxin *Protein binding is decreased by dialysis; volume of distribution reduced by uremia*	Hepatic (renal)	144-200/210	94	0.6	D	Unchanged	50-75	No (He, PD)
Digoxin *Radioimmunoassay may overestimate serum levels in uremia; clearance reduced by spironolactone, quinidine, verapamil; hypokalemia, hypomagnesemia enhance toxicity; volume of distribution decreased in ESRD; serum level 12 hours after first dose is best guide in ESRD*	Renal (Nonrenal 15%-40%)	36-44/80-120	20-30	5-8	D, I	25-75 every 36 h	10-25 every 48 h	No (He, PD)

ESRD = end-stage renal disease, GFR = glomerular filtration rate, HCl = hydrochloride, He = hemodialysis, PD = peritoneal dialysis

ing physician knows the therapeutic drug concentration desired and which levels are considered toxic, drug level monitoring can greatly enhance individualized therapy, especially in patients with renal failure. Drug concentrations are commonly determined from serum specimens, but occasionally plasma or whole blood concentrations are required. Interpreting drug concentrations requires a knowledge of the exact dose given, the route of drug administration, the elapsed time from the last dose, and the drug's elimination half-life in a specific patient. Drug concentrations may be used after an appropriate loading dose or three to four maintenance doses have been administered to assure that steady-state concentrations have been achieved. Peak levels reflect the highest drug concentration achieved after an initial rapid distribution phase and are measured 30 to 60 minutes after parenteral administration or one to two hours after oral ingestion. Peak values tend to correlate with drug efficacy. Trough levels, on the other hand, should be measured immediately before the next dose to indicate the lowest concentration of drug in the body and thus systemic clearance. Drug trough values tend to be used as indicators of toxicity.

The interpretation of drug levels must include clinical evaluation because toxicity can occur with levels within the "therapeutic" range. For example, digitalis intoxication can occur in the presence of therapeutic serum levels if hypokalemia or metabolic alkalosis coexists. An increase in the unbound or biologically active fraction of a given drug may not be reflected in drug level monitoring because most assays measure total drug concentration (protein-bound plus unbound fractions). This point is illustrated by phenytoin, which is highly protein-bound under normal circumstances. In hypoalbuminemic patients such as those with the nephrotic syndrome or in uremic states, the protein-bound fraction of phenytoin is substantially reduced but the unbound or biologically active fraction is increased. In addition, the increased free form of phenytoin leads to increased hepatic metabolism. Thus, it is prudent to measure free phenytoin concentrations in uremic or hypoalbuminemic patients because "therapeutic" levels of total drug might mask toxic or subtherapeutic levels of unbound drug.

Dialysis and Drug Dosing

Patients undergoing dialysis treatment require special attention with regard to dose scheduling and the possible need for supplemental dosing for agents substantially cleared by dialysis. Factors affecting dialysis drug clearance are listed in Table 3. The molecular weight, water solubility, and degree of protein binding for any given drug represent the major determinants of its dialyzability. The smaller (less than 500 daltons), the more hydrophilic, and the less protein-bound a compound is, the greater the clearance by dialysis treatments. Continuous hemofiltration methods are becoming increasingly common in intensive care units, and an awareness of drug removal by these procedures is essential. Solutes and pharmacologic agents are removed by convective transport in hemofiltration procedures. Thus, any compound distributed in plasma water and not highly protein-bound will cross hemofiltration membranes, appearing in the ultrafiltrate. When the filtrate generated by hemofiltration is adequate to correct uremia and a drug is less than 60% protein-bound, sufficient drug removal will be likely and supplemental dosing warranted.

In summary, responses to drug therapy in patients with renal failure are markedly heterogeneous and require thoughtful consideration and ongoing evaluation by prescribing physicians. Although reductions in glomerular filtration rates can be factored mathematically into dosage-adjustment strategies, this merely represents the initial step and one of many pharmacokinetic and metabolic principles to be considered. Dosing information such as that provided in Table 2 must be applied to individual patients in a prudent manner, taking into account specific alterations in drug handling induced by the degree of renal impairment and any other concurrent conditions.

TABLE 3.—*Factors Affecting Dialysis Drug Clearance*

Drug properties
Molecular weight
Charge
Water solubility
Volume of distribution
Dialyzer membrane binding
Erythrocyte partitioning
Nonrenal excretory pathways
Membrane properties
Blood flow
Pore size
Vascular disease (peritoneal dialysis)
Surface area
Fluid films
Loculation/sclerosis (peritoneal dialysis)
Dialysate properties
Flow rate
Solute composition
Volume (peritoneal dialysis)
Temperature
pH
Miscellaneous
Convective transport during ultrafiltration

Suggested Reading

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Autoimmune Disease and the Nervous System
Biochemical, Molecular, and Clinical Update

Moderator
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Discussants
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This is an edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is Anthony T. Campagnoni, PhD, Professor of Medicine.

Autoimmunity in the central and peripheral nervous system can manifest as the result of cellular or humoral immune responses to autoantigens. There is evidence that multiple sclerosis is a cell-mediated autoimmune disease of the central nervous system in which both myelin and the cell that produces the myelin are destroyed. Diseases such as acute inflammatory demyelinating polyneuropathy (also called Guillain-Barré syndrome) and myasthenia gravis are considered antibody-mediated diseases of the peripheral nervous system and neuromuscular junctions, respectively. We review these diseases and explore mechanisms of immune-mediated destruction of these nervous system components. We specifically focus on one effective therapy aimed at countering the immune attack, that of thymectomy in patients with myasthenia gravis.

(Merrill JE, Graves MC, Mulder DG: Autoimmune disease and the nervous system—Biochemical, molecular, and clinical update. West J Med 1992 Jun; 156:639-646)

JEAN E. MERRILL, PhD*: Multiple sclerosis is a demyelinating disease of the white matter of the central nervous system (CNS) in which myelin and the myelin-producing macroglia cell, the oligodendrocyte, are destroyed. Axons are usually spared. In response to the damage, macroglial astrocytes in the central nervous system undergo proliferation and hypertrophy, which is called astrogliosis.[1] Multiple sclerosis is thought to be an autoimmune disease for reasons that will be discussed.† Both blood-borne inflammatory cells and endogenous glial cells (astrocytes as well as brain macrophages called microglia) have been implicated in the disease process.[2-4] Several abnormalities have been documented in subsets and functions of lymphocyte subpopulations[2,5-7] and will not be discussed here. Multiple sclerosis is diagnosed by neurologic examination, laboratory studies of immunoglobulins in cerebrospinal fluid (CSF), and, more recently, noninvasive magnetic resonance imaging.[2-4]

The Trimolecular Complex

The three components of the trimolecular complex that seem to be most critical for autoimmune disease, or reactivity to self-antigens, are the major histocompatibility complex, class II molecules (MHC or HLA-DR) expressed on various antigen-presenting cells, the antigenic peptide, and the T-cell receptor on $CD4^+$ T-cell subsets.[8-10] In the animal model for multiple sclerosis, experimental allergic encephalomyelitis (EAE), specific encephalitogenic peptides from the myelin constituent myelin basic protein, when presented on restricted MHC-II molecules in susceptible murine strains, induce highly restricted T-cell receptor variable region genes on $CD4^+$ cells.[11-14] In multiple sclerosis, we have less information regarding these three molecules. The MHC-II molecules DR2 and DRw2 are overrepresented in patients with multiple sclerosis.[2,15] The MHC-II molecules in multiple sclerosis are expressed on endothelial cells of the blood-brain barrier, on microglia and astrocytes, and on inflammatory macrophages.[16-19] Any of these cells could behave as antigen-presenting cells to present self-antigen to $CD4^+$ T cells.

The antigen that induces or perpetuates, or both, the chronicity of the disease is unknown. Epidemiologic and demographic studies suggest an exogenous infectious agent, such as a virus, as a candidate immunogen. Tolerance to self would then be broken either by viral alteration of a normal self-antigen through infection of a brain cell or through a cross reactivity called molecular mimicry in which the viral antigen resembles a normal brain antigen.[20] In addition, an imbalance in the immune system T-cell subsets in patients with multiple sclerosis is thought to play a part in inducing disease. A functional or numerical increase in $CD4^+$ helper-inducer T cells (cells that mediate delayed-type hypersensitivity) and a decrease in $CD8^+$ suppressor-cytotoxic T cells have been shown to occur in patients with multiple sclerosis. $CD4^+$ cells exposed to the correct autoreactive or cross-reactive antigen, presented by restricted MHC-II molecules, would then give rise to autoimmunity.[2,13,15]

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†See also "Autoimmune Disease and the Nervous System," by L. Steinman, MD, pages 664-666 of this issue.

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ABBREVIATIONS USED IN TEXT

AChR = acetylcholine receptor
CMV = cytomegalovirus
CNS = central nervous system
CSF = cerebrospinal fluid
EAE = experimental allergic encephalomyelitis
IFN-γ = interferon gamma
IL = interleukin
MHC = major histocompatibility complex
TGF = transforming growth factor
TNF = tumor necrosis factor

T Lymphocytes and Interleukin 2

Activated T cells from peripheral blood, whether they are specific to brain antigens or not, can and do cross into the CNS through an intact blood-brain barrier.[21] The mechanisms by which this occurs are not known. If these activated T cells recognize antigens in the brain, they can cause damage in the CNS. Measurement and detection using various techniques have shown that the $CD4^+$ T cells predominate over the $CD8^+$ T cells in the lesion, spinal fluid, and blood of patients with multiple sclerosis.[17,22-27] The $CD4^+$ cells are activated in that they express MHC-II, a T-cell differentiation marker (TA-1), and interleukin (IL)-2 receptors (TAC) and produce cytokines.[17,24-26] Some of these cells respond to brain antigens.[22,26,28] In addition, although there may be some restriction in gene usage in the T-cell receptor in multiple sclerosis,[23,29,30] it is not as limited in heterogeneity as is found in the EAE model.[7-9]

Elevated levels of IL-2 and IL-2R have been detected in CSF and serum of patients with multiple sclerosis,[31-38] as well as in tissue.[17] Serum levels of IL-2 correlate inversely with disability and directly with a poor prognosis.[34] In patients with chronic disease, the magnitude of the initial IL-2 levels varies inversely with the duration of disease and predicts subsequent worsening.[37] An association of T cells capable of producing and responding to IL-2 and disease duration, worsening, or both, implies that interleukin 2 is expanding encephalitogenic clones in the periphery and locally in the CNS. Thus, although this is not unique to patients with multiple sclerosis in that other autoimmune and inflammatory diseases show similar findings, it is indicative of an activated response of the immune system that may correlate with the fluctuations in symptoms.

Interferon Gamma and Major Histocompatibility Complex Class II Molecules

Interferon gamma (IFN-γ) can induce or increase the expression of MHC-II molecules on T cells, macrophages, microglia, and astrocytes either directly or indirectly through the induction of tumor necrosis factor (TNF) α.[39-43] Interferon gamma and MHC-II, although not expressed in normal brain, are expressed in multiple sclerosis plaques, and the staining for these is associated with macrophages and astrocytes in lesions.[17,18,44] In recent studies, T cells of patients with multiple sclerosis stimulated in vitro were shown to produce increased amounts of IFN-γ compared with T cells of control subjects.[45-47] Interferon gamma is also detectable in the CSF of patients with multiple sclerosis. Activation of the immune system in patients with multiple sclerosis by clinical treatment with IFN-γ leads to exacerbations and an increase in circulating MHC-II–positive macrophages.[48,49]

Macrophages and Cytokines

Prostaglandin E, interleukin 1, and tumor necrosis factor-α. Macrophages in blood, CSF, and brain of patients with multiple sclerosis are activated. They have been shown to actively cap immunoglobulin on myelinated nerve fibers at plaque margins[50] and to produce prostaglandin E and IL-1 at the blood-brain barrier and in the lesion.[17] Prostaglandin E levels are elevated in the CSF of patients with multiple sclerosis and in vitro in cultures of stimulated blood macrophages.[51,52] In multiple sclerosis, macrophages show increased oxygen burst in vitro and the CSF contains autooxidative products of degraded membrane phospholipids, both of which are consistent with lipid peroxidation and myelin destruction.[53,55] Interleukin 1 and TNFα coinduce each other and stimulate the production of prostaglandin E,[56-59] which regulates temperature and fever.[56-58] Because patients with multiple sclerosis show a worsening in neurologic status during febrile episodes,[60] IL-1, TNFα, and prostaglandin E may contribute to the disease process through fever induction. In vitro studies in multiple sclerosis have confirmed that production by macrophages of IL-1[61-63] and TNFα[46] is elevated. Both macrophages and glial cells are associated with these cytokines in situ in the lesions.[64]

Examination of serum and CSF specimens for such cytokines as IL-1, IL-6, and TNF has led to less clear findings of undetectable, elevated, or normal levels of cytokines compared with levels in fluids from control subjects.[63,65-68] Some of the confounding problems in measuring cytokines in biologic fluids from patients and correlating the results with their disease are the short half-life of these proteins, the concomitant production and presence of inhibitors, and the possible induction in vivo by bacterial infections unrelated to the disease process of interest.

TABLE 1.—*Putative Roles for Cytokines in Demyelinating Disease*

Cytokine	*Possible Function in Multiple Sclerosis*
Interleukin (IL)-1 + TNFα	Astrogliosis Microgliosis Oligodendrocyte cell death Induction of fever and decreased electric conductivity along demyelinated fiber
Interferon gamma	Increased MHC-II on macrophages, T cells, microglia, and astrocytes Increased cytotoxicity by macrophages and microglia Increased permeability of blood-brain barrier
Transforming growth factor β	Decreased function of IL-1 and TNFα Inhibition of function of activated macrophages Inhibition of T-cell response to IL-2

TNFα = tumor necrosis factor-α

Role of interleukin 1 and tumor necrosis factor-α in lesion formation. Astrocytes produce IL-1 and TNF and respond to these cytokines by proliferation and differentiation.[69-75] It is not clear whether the response is direct or indirect through the induction of other factors or cytokines by IL-1 and TNFα.[74,75] Nevertheless, the effects of these cytokines, direct or indirect, could lead to astrogliosis and plaque formation in multiple sclerosis. The damage to myelin and the oligodendrocyte has long been thought to be the result of activated inflammatory blood macrophages and endogenous microglia.[1,15,19,76,77] Both TNFα[78,79] and IL-1[75] have been implicated. It is not certain, however, whether microglia- or

macrophage-bound membrane cytokines or their soluble counterparts—as in the case of TNFα—are responsible for the death of oligodendrocytes.[76] Of interest, transforming growth factor (TGF) β, a cytokine that inhibits the biologic function of IL-1 and TNFα,[80] also inhibits microglial cytotoxicity of oligodendrocytes.[76] The use of TGFβ effectively treats and prevents EAE in vivo in animals.[81] The putative roles for cytokines in demyelinating disease are shown in Table 1.

Therapy for Multiple Sclerosis

Immunointervention in multiple sclerosis has been generally targeted at various elements of the immune response and particularly at components of the trimolecular structure. Earlier therapeutic protocols using immunosuppressive drugs resulted in modest improvement but proved to be somewhat disappointing because of their nonspecificity, inefficiency, or toxicity.[82-85] Although active vaccination to the T-cell receptor on autoreactive T cells in the EAE model has proved efficient at preventing disease,[86] such preliminary studies have just begun in multiple sclerosis and may prove difficult.[87] The passive administration of antibody to block the T-cell receptor MHC-II molecules and ancillary T-cell molecules like CD4 and CD3 or cytokine receptors has been contemplated[88] and actually carried out in some patients.[89]

The use of natural antagonists to cytokines has proved to be a promising approach. The use of TGFβ might inhibit IL-1 and TNFα production in patients with multiple sclerosis.[76,80,81] Interferons alfa and beta, natural antagonists of the immunologically mediated actions of IFN-γ, have ameliorating effects in vivo in multiple sclerosis.[90-92] The mechanisms of this beneficial effect are thought to be the following: the inhibition of IFN-γ-induced MHC-II by IFN-β,[93] which would inhibit antigen presentations by antigen-presenting cells; a reversal of nonspecific suppression in multiple sclerosis[94]; and the inhibition of IFN-γ secretion by T cells in multiple sclerosis.[95]

Antibody-Mediated Neurologic Diseases

MICHAEL C. GRAVES, MD*: The motor unit is the final common pathway for the activation and control of muscular movement. A typical motor unit consists of an anterior horn cell body, its myelinated axon, and the collection of muscle cells innervated by terminal branches of the axon.

Table 2 summarizes some diseases with symptoms caused by dysfunction at various parts of the motor unit. In myasthenia gravis and myasthenic syndrome, antibodies directed at specific ion channels are the cause of the disease. The other conditions listed in Table 2 have defects located at other specific points along the motor unit, and they also have at least some characteristics common to myasthenia and other autoimmune diseases.

The following findings are common for the better characterized autoimmune diseases such as myasthenia gravis and may offer clues to the pathogenesis of the other conditions:

- An antibody is directed at a specific target, which can explain the pathophysiology of the disease;
- The antibody is present in patients but not controls;
- The disease can be transferred to an experimental host using antibody;
- Symptoms can be lessened with immunosuppressive treatment or plasmapheresis;
- The diseases are commonly associated with other autoimmune diseases; and
- The diseases may be associated with neoplasms.

Two or more of these characteristics are present for all of the diseases listed in Table 2. Specific antibody directed at the presynaptic and postsynaptic sides of the myoneural junction explain the pathophysiology of myasthenic syndrome and myasthenia gravis, respectively; these antibodies can also transfer the disease to laboratory animals. Antibodies directed at myelin are found in demyelinating inflammatory polyneuropathies, and antibodies directed at neuronal gangliosides are present in axonal neuropathies. The latter are sometimes present in other conditions, however, and experiments for the passive transfer of the neuropathy with serum have not yet been done. Associations with other autoimmune diseases are known for myasthenia and for demyelinating neuropathies. Myasthenia gravis, myasthenic syndrome, and the "stiff-man" syndrome are associated with tumors. All of these diseases have been treated with corticosteroids, plasmapheresis, or other immunosuppressive treatments with at least some degree of success.

TABLE 2.—*Motor Unit Dysfunction in Autoimmune Neuromuscular Diseases*

Location of Dysfunction	*Disease*
Inhibitory interneurons	"Stiff-man" syndrome
Peripheral nerve axons	Axonal neuropathies
Peripheral nerve myelin	Demyelinating neuropathies
Myoneural junction	
Presynaptic	Myasthenic syndrome
Postsynaptic	Myasthenia gravis

'Stiff-Man' Syndrome

The stiff-man syndrome is a rare condition of continuous muscle activity at rest.[96] Some patients have stiffness of one or more limbs but continue to function. In more severely affected patients, the condition is similar to tetanus or strychnine poisoning, with incapacitating rigidity and muscle spasms, respiratory failure, fever, elevations of serum creatine kinase levels, and a remarkable response to benzodiazepine medications.[97,98] These findings suggest dysfunction of an important inhibitory synapse on the motor neuron. The presence of antibodies to glutamic acid decarboxylase, an enzyme that produces the inhibitory neurotransmitter γ-aminobutyric acid, has been reported and seems to explain the motor unit activity that characterizes the syndrome,[99] but the antibodies have not been found by other investigators.[100] More recent reports of autoantibodies reactive with neurons containing γ-aminobutyric acid, if confirmed, would certainly explain the pathophysiology of the syndrome.[101] Patients often have pleocytosis and elevated levels of IgG in cerebrospinal fluid. The association with diabetes may relate to the presence of antibodies to pancreatic beta cells.[101] The association with neoplasms may also be an indirect indication of autoimmunity. Severely affected patients have benefited from treatment with corticosteroids or plasmapheresis.[102]

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Motor Neuron Diseases

Motor neuron diseases are conditions characterized by a loss of motor neurons with resultant muscle weakness and atrophy. In typical cases of amyotrophic lateral sclerosis, both the corticospinal and the anterior horn cells degenerate, causing a mixture of upper and lower motor neuron signs.[103] Bulbar involvement may lead to dysphagia and dysarthria. The presence of antibodies directed at neuronal gangliosides, and occasionally of IgM paraproteins, has renewed interest in an autoimmune cause for amyotrophic lateral sclerosis. Drachman and Kuncl coined the term "unconventional autoimmune disease" to emphasize that any autoimmune cause for amyotrophic lateral sclerosis will be unique and different from the causes of conventional autoimmune diseases such as myasthenia.[104] A useful immunosuppressive treatment for most cases of amyotrophic lateral sclerosis has not yet evolved. Occasional anecdotal and sometimes published atypical cases of motor neuron diseases have shown favorable response to immunosuppression, however.

Patients with the following characteristics may represent a subtype of motor neuron disease: lack of upper motor neuron involvement, lack of bulbar involvement, conduction block of motor axons on nerve conduction studies, and high levels of antibodies directed at the GM-1 ganglioside or at other related glycolipids.[105,106] Some of these patients have IgM paraproteins directed at the ganglioside antigens. Immunosuppressive treatment has been reported to benefit some patients with these characteristics. In some cases, initial treatment with corticosteroids, azathioprine, and apheresis has not been helpful, but benefit has been reported with the use of cyclophosphamide.[107] The IgM antibodies directed at gangliosides seem to be difficult to suppress with treatments that have been successful in myasthenia and other autoimmune disorders.[107,108]

Acute Inflammatory Demyelinating Polyneuropathy

Acute inflammatory demyelinating polyneuropathy, also known as the Guillain-Barré syndrome, is a paralytic condition caused by immune-mediated demyelination of peripheral nerve.[109] Acute inflammatory demyelinating polyneuropathy may be associated with antecedent viral infection. Chronic inflammatory demyelinating polyneuropathy follows a chronic worsening or a relapsing remitting clinical course.[110] Antibodies to myelin and to specific carbohydrate structures of glycolipids and glycoproteins have been reported in patients with these diseases.[109] These antibodies are generally IgM. Occasionally patients with monoclonal gammopathies directed at similar determinants have a similar demyelinating polyneuropathy.[111,112] Experimental microinjection of patients' serum can demyelinate nerves of experimental animals.[113] Treatment with plasmapheresis is effective in both acute and chronic inflammatory demyelinating polyneuropathies, and corticosteroids or immune suppression is effective treatment of the chronic disorder.

Myasthenia Gravis

Myasthenia gravis is a disease of weakness and fatigue, frequently affecting swallowing, speech, eye movements, and facial muscles.[114] Antibodies directed at acetylcholine receptor (AChR) are present in most patients, and evidence for the passive transfer of transient myasthenia to newborns of myasthenic mothers has long been appreciated. Passive transfer with patients' IgG or with monoclonal antibodies to the receptor is further evidence for an autoimmune antibody-mediated mechanism.[115] The effect of these antibodies is a simplification of the normally richly enfolded subsynaptic membrane and a reduction of the amount of AChR. The AChR is a sodium channel that opens to generate a transient end-plate potential in response to a quantity of acetylcholine released by the nerve terminal. A reduction in the membrane concentration of AChR causes a reduction in both the rate of rise and the height of the end-plate potential. This leads to a slight time delay in the muscle membrane action potential, a phenomenon known as jitter, which is measurable in the electromyographic laboratory.[116] Occasionally the end-plate potential fails to reach threshold and that muscle fiber fails to contract. The statistical failure of a large number of such fibers in time is the basis for weakness and fatigue in a patient with myasthenia.

The treatment of myasthenia is gratifying to clinicians.[114-117] Anticholinesterase medications can control many of the symptoms and are sufficient treatment in many cases. Corticosteroids and occasionally azathioprine or other immunosuppressive medications are used when needed. Patients in crisis may need mechanical ventilation and tube feeding, and plasmapheresis provides the most rapid improvement. Thymectomy has been an important treatment since the 1940s. The thymus gland is frequently enlarged for age in patients with myasthenia. The occurrence of thymomas is also well recognized in this disease. The rationale for thymectomy and some of our experience at UCLA are described in detail.

The Myasthenic Syndrome

The myasthenic syndrome, or the Lambert-Eaton myasthenic syndrome, is another antibody-mediated disease of neuromuscular transmission.[118] In this disorder, antibodies are directed at voltage-dependent calcium channels on the presynaptic nerve terminals, which are necessary for the coupling of the depolarization of the nerve terminal to the release of acetylcholine. This reduction in acetylcholine release can be partially and transiently overcome by a rapid volley of nerve impulses—for example, after a brief isometric contraction. This potentiation is easily shown in the laboratory by measuring the compound action-potential response of muscle to a single nerve stimulation before and after 15 seconds of isometric contraction. The physiologic defect of the Lambert-Eaton myasthenic syndrome can be transferred passively to experimental animals with serum, and patients improve with either immune suppression or plasmapheresis. The syndrome is strongly associated with small-cell carcinoma of the lungs, especially in smokers. Small-cell carcinoma is neurodermally derived and contains the same type of calcium channels that are present in the motor nerve terminals.

Causes of Autoimmunity

The effects of various autoantibodies directed at each specific site of the motor unit cause the specific diseases just described. Why are these autoantibodies formed? If we knew the primary cause of the induction of these autoantibodies, we might devise better and more specific treatments.

What induces autoantibodies? There are three relevant areas of research: the genetics of the immune response, the immune networks, and the thymus in patients with myasthenia gravis.

Like a number of other autoimmune diseases, myasthenia gravis is associated with a higher-than-expected frequency of certain HLA haplotypes.[119,120] There is no simple genetic inheritance of myasthenia or other autoimmune diseases. Probably a number of genetic loci, possibly including B- and T-cell receptor genes, immunoglobulin variable region genes, and class I, II, and III MHC molecules, play a cumulative role in determining susceptibility to these conditions, as suggested by Newsom-Davis and co-workers for myasthenia gravis.[119] The associations of myasthenia with these and other markers suggest that there are genes that enhance the ability to produce the autoantibodies of myasthenia. So far there is little or no evidence for such associations in other diseases discussed in this section.

The immune network theory provides a framework for the production of anti-idiotypic (anti-Id) antibodies that may cross-react with autoantigens.[121] For example, anti-Id antibodies directed against some primary antimicrobial antibodies have anti-AChR activity.[122] This suggests a mechanism for the induction of the anticarbohydrate antibodies associated with motor neuron diseases and with demyelinating autoimmune neuropathies. Many viruses use cell-surface carbohydrates as receptors. Viruses may attach to the same carbohydrate structures recognized by the autoantibodies of these neurologic diseases. The proposed mechanism is that the virus recognizes the cell-surface receptor, the viral infection induces the antiviral antibody, the antiviral antibody recognizes the receptor binding site on the virus, the anti-Id antibody is produced against the antiviral antibody, and the anti-Id antibody cross-reacts with the cell-surface receptor and becomes an autoantibody.

There are many examples of this mechanism in which immunization with a virus, a hormone, or a drug induces antibodies directed at the cellular receptor for the virus, hormone, or drug.[123] We have evidence that the mechanism can operate in an experimental system of relevance to autoimmune neurologic disease.

Cytomegalovirus and Autoimmunity

Cytomegalovirus (CMV) is one of the most common viruses associated with the Guillain-Barré syndrome. The timing of paralysis suggests a postinfectious mechanism. Autoantibodies are found in human CMV infection and in experimental murine CMV infection of mice.[124] We studied the structure of the host-cell receptor for murine CMV. Attenuated murine CMV specifically recognizes the sequence of the sugars *N*-acetylglucosamine-galactose.[125] This is similar to the antigens of autoimmune demyelinating neuropathies. In experimental infection, mice first produce antiviral antibodies, with peak production at 21 days. At 36 days postinfection, antibodies directed at the receptor also appear. Analysis of a panel of antiviral and antireceptor monoclonal antibodies from mice indicated that some antibodies are produced that are antireceptor autoantibodies and are also anti-Id antibodies (react with the antiviral antibodies), as predicted by the mechanism just described. The identity of the human CMV receptor is not yet known, but it is possible that human CMV and other human viruses may induce autoantibodies by the type of anti-Id mechanism that we have shown in mice.

The Thymus in Myasthenia Gravis

In patients with myasthenia gravis, the thymus is frequently enlarged, and there is also an increased incidence of thymoma. The removal of the thymus is associated with an improved prognosis.[126] It has been estimated that the thymus is the source of a significant but small portion of anti-AChR production in patients. The presence of AChR-bearing myoepithelial cells in close proximity to immune lymphocytes in the thymus has been proposed as the milieu in which autoimmunity is induced.[119] Thymectomy is thus a strategy for potentially intervening early in the process of the induction of autoimmunity.

Role of Thymectomy in Myasthenia Gravis

DONALD G. MULDER, MD*: Nerve impulse transmission to muscle occurs at the acetylcholine receptor site by the release of acetylcholine, which is counterbalanced appropriately by postsynaptic cholinesterase. In patients with myasthenia gravis, many of these receptor sites are blocked, bound, or degraded by antibodies induced by events arising in the patients' own thymus glands. As a result of this autoimmune process, patients have a decreased number of normally functioning neuromuscular units and have symptoms of weakness and easy fatigability.

There are four ways that a myasthenic patient can be managed:

- Anticholinesterase medications, the most common being pyridostigmine bromide (Mestinon), to enhance the acetylcholine effect on the remaining functioning AChR;
- Immunosuppressive drugs, such as prednisone and azathioprine, to control the immune response;
- Plasmapheresis treatments to transiently decrease the amount of circulating antibody; and
- Thymectomy to remove the source of autoantibody induction.

Indications for Operation

In recent years we have recommended thymectomy earlier in the course of the disease for several reasons: surgical morbidity and mortality are low; many patients have progression of symptoms despite increasing dosages of anticholinesterase medications; intolerance to medications develops, especially as the dosages are increased; long-term side effects and complications of steroid therapy develop; plasmapheresis produces only a transient benefit; and reversibility of impaired function at the AChR sites becomes a concern once they have become blocked or bound by antibody. Even if spontaneous improvement should occur, it is known that such improvement or even remission is uncommon and short-lived.

Thus, the clinical diagnosis of myasthenia gravis—substantiated unequivocally by a positive test with edrophonium bromide (Tensilon), frequently (85%) with the finding of receptor site antibodies in the serum, and abnormal single fiber electromyography—warrants consideration of thymectomy even in those patients with ocular and mild generalized disease. The finding on routine chest roentgenograms of an anterior mediastinal mass, further delineated by a computed tomographic scan or magnetic resonance imaging, and the presence of antistriational muscle antibody (90%) provide strong evidence for the diagnosis of thymoma. The presence of a thymoma, which occurs in approximately 20% of patients with myasthenia, is another indication for operation.

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Perioperative Considerations

Most patients can be operated on when their symptoms are stable and under satisfactory medical control. In those with rapidly progressive disease that is difficult to control, the use of plasmapheresis has been of great help in stabilizing patients before an operation. Because only about 40% of the receptor site antibody is present in the serum at any one time, multiple treatments (weekly for four to six weeks) may be necessary to achieve the desired results. The transient but usually dramatic improvement in a patient's condition permits a much safer operation.

Total thymectomy is done through a median sternotomy incision, which gives optimum exposure to the bilobed structure lying directly behind the sternum. The lateral margins approach the phrenic nerves, which are carefully spared from injury as the entire gland and all mediastinal fat—which occasionally harbors aberrant remnants of thymic tissue—are removed. The cervical pedicles of the thymus, which are frequently contiguous with the inferior pole of the thyroid, are also removed.

Any thymoma should be excised with a generous margin of contiguous tissue and the entire thymus gland removed as well. Locally invasive thymomas should be managed aggressively by block resection of involved pericardium, lungs, and vascular structures because the results of surgical removal supplemented by irradiation, chemotherapy, or both, are surprisingly good.

Because many patients have limited ventilatory reserve, their anesthetic management and postoperative care are extremely important to minimize pulmonary complications. Most patients can be extubated in the immediate postoperative period, whereas some must be carefully weaned from the respirator after one or two days. A tracheostomy has rarely been necessary.

TABLE 3.—*Results of Thymectomy in 333 Patients With Myasthenia Gravis From 1954 to 1987*

	Patients					
	Men		Women		Total	
Result	No.	(%)	No.	(%)	No.	(%)
Remission	35	(38)	121	(50)	156	(47)
Improved	38	(41)	89	(37)	127	(38)
Operation benefited	73	(78)	210	(88)	283	(85)
Same	10		22		32	
Worse	1		1		2	
Dead*	9		7		16	
Total	93		240		333	

*2 operative deaths; mean follow-up 6.45 yr.

Results After Thymectomy

In recent years thymectomy has gained increasing acceptance as the most effective therapy for achieving sustained improvement in most patients with myasthenia gravis.[127-130] We reported our results at the UCLA Medical Center in 1983 with 249 patients[127] and again in 1989 with an additional 84 patients.[126] This 33-year experience with 333 patients is summarized in Table 3. Remission—no medication, no symptoms—was achieved in 121 of the 240 women (50%) and 35 of the 93 men (38%). Improvement—less medication, fewer symptoms—was noted in an additional 37% of the women and 41% of the men. Overall, 283 of the 333 patients (85%) benefited from the operation. Reoperation for recurrent invasive thymoma resulted in two operative deaths. Over a mean follow-up period of 6.45 years, there were 14 late deaths, which in most instances were caused by complications related to a progression or relapse of the patients' myasthenia.

An attempt was made in the recent five-year review of our experience[126] to identify factors that might predict a more favorable outcome after thymectomy. The presence of AChR antibodies in the patients' serum and a thymus gland containing areas of hyperplasia were found to be predictors of a favorable outcome.

Serum for determining AChR antibody levels was obtained from 76 of the 84 patients in the recent series. Antibodies were detected in 43 patients, of whom 19 (44%) achieved remission and 21 had improvement; hence, 40 patients (93%) benefited from the operation. In contrast, only 21 (64%) of the 33 patients in whom no antibody was detectable benefited from the operation. Nine (27%) achieved remission, and 12 showed improvement.

The presence of hyperplasia in the excised thymus gland was noted in 38 patients, of whom 20 (53%) achieved remission and 13 had improvement; hence, 33 (87%) benefited from the operation. A normal gland—one without specific diagnostic changes, such as atrophy or involution—was found in 35 patients and was associated with remission in 7 (20%) and improvement in 17, so that 24 patients (69%) benefited from the operation.

In the 11 patients with thymoma, 10 (90%) benefited from the operation in which the thymoma and all remaining thymus were excised. Three patients (27%) had remission and seven improved postoperatively.

The combination of hyperplasia of the thymus gland and the presence of AChR antibodies was a favorable prognosticator (Table 4). Of the 23 patients with this combination, 15 achieved remission (65%) and 7 had improvement; hence, 22 (96%) of the 23 benefited from the operation. In contrast, the 22 patients without AChR antibodies and without hyperplasia did not have as favorable a response; 14 (64%) benefited from the operation, and only 6 (27%) had remission.

TABLE 4.—*Thymus Disease and Acetylcholine Receptor Antibodies After Thymectomy in 76 Patients With Myasthenia Gravis From 1982 to 1987*

	Patients						
	Total	Remission		Improved		Benefited From Operation	
Disease and Antibody (Ab) Status	No.	No.	(%)	No.	(%)	No.	(%)
Hyperplasia, Ab+	23	15	(65)	7	(30)	22	(96)
Hyperplasia, Ab−	11	3	(27)	4	(36)	7	(64)
No diagnostic changes, Ab+	10	1	(10)	8	(80)	9	(90)
No diagnostic changes, Ab−	22	6	(27)*	8	(36)	14	(64)*
Thymoma, Ab+	10	3	(30)	7	(70)	10	(100)

+ = positive, − = negative

*Difference between categories is $P<.05$.

Of the 11 patients with thymoma, all 10 with AChR antibodies benefited from the operation. Three patients (30%) achieved remission.

Based on our experience and that of others, it can be said that thymectomy is beneficial to most patients with myasthenia gravis. The operation has a low morbidity and mortality.

Although the outcome is not entirely predictable for any specific patients, predictors of success are a relatively young age with less severe disease of short duration in a patient who does not have an invasive thymoma but who has hyperplasia of the thymus and the presence of anti-AChR antibodies preoperatively.

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Epitomes

Important Advances in Clinical Medicine

Obstetrics and Gynecology

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in obstetrics and gynecology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Diabetes Mellitus in Pregnancy

DIABETES MELLITUS or glucose intolerance in pregnancy carries substantial risk to both mother and fetus. Maternal risks include increased rates of pregnancy-induced hypertension, cesarean section with attendant morbidity, and polyhydramnios and spontaneous abortion. Fetal risks include developmental anomalies, birth trauma, and intrauterine asphyxia and death. The newborns of diabetic women are subject to hypoglycemia, hyperbilirubinemia, and electrolyte disturbances, especially of calcium levels. Female newborns are at an increased risk of having glucose intolerance in future pregnancies.

Whereas the diagnosis is obvious in women who are already insulin-dependent, carbohydrate intolerance would be undetected without the appropriate screening evaluation in the majority of at-risk pregnant women. By definition, gestational diabetes is carbohydrate intolerance of variable severity, first occurring or first being recognized during pregnancy. All pregnant women should have a plasma glucose determination an hour after consuming 50 grams of glucose as a flavored solution. Testing is usually done at 28 weeks of gestation. Pregnant women with "high-risk" factors such as previous stillbirth, a previous infant with a congenital anomaly, or a previous macrosomatic infant (greater than 4,500 grams) should be tested at the first prenatal visit. If testing results are normal, the test should be repeated at 28 weeks of gestation. Values greater than 7.8 mmol per liter (140 mg per dl) require a formal three-hour glucose tolerance test. After fasting and baseline sampling, 100 grams of glucose is taken. Normal plasma glucose values are as follows: fasting, less than 5.7 mmol per liter (105 mg per dl); after one hour, less than 10.5 mmol per liter (190 mg per dl); after two hours, less than 9.2 mmol per liter (165 mg per dl); and after three hours, less than 8.0 mmol per liter (145 mg per dl). Two abnormal values constitute carbohydrate intolerance and a diagnosis of gestational diabetes.

Maternal morbidity is greatly reduced in women with gestational diabetes when a comprehensive management plan is developed by the primary care physician in consultation with a perinatologist. The plan should begin with diet counseling, education, and glucose monitoring. Insulin therapy is indicated when fasting and postprandial glucose determinations are persistently greater than 5.7 and 6.7 mmol per liter (105 and 120 mg per dl), respectively.

Perinatal morbidity and mortality are reduced through close fetal surveillance in the third trimester in pregnant women who are insulin-dependent. Testing for fetal well-being should be started at 32 weeks of gestation. The fetal nonstress test, in combination with amniotic fluid volume assessment, should be done two to three times a week. The nonstress test evaluates the fetal heart rate response to fetal movement during a 20-minute recording of the fetal heart rate. Accelerations of the fetal heart rate with fetal movement suggest no compromise of fetal well-being. The absence of accelerations of the fetal heart rate or decelerations suggest fetal compromise and require further testing. The fetus may be "stressed" by inducing uterine contractions and the heart rate response evaluated. If no fetal heart rate decelerations occur with three contractions spaced two to three minutes apart, fetal well-being is established. Amniotic fluid volume is determined with the use of ultrasonography. Fluid pockets are measured in each of the four quadrants of the amniotic cavity and then totaled as the "amniotic fluid index." An index greater than 5 cm is considered normal. As an alternative to stressing the fetus, when the nonstress test results are abnormal, an ultrasound evaluation for fetal breathing movement, fetal tone, and fetal movement may be used. Two of these three variables as seen on ultrasonogram, along with a normal amniotic fluid index, are consistent with good fetal status. Estimates of fetal weight by ultrasonogram at three-week intervals enhance the ability to diagnose fetal macrosomatia.

There is no uniform agreement in the approach to fetal surveillance in pregnant women whose diabetes is well controlled with diet. Data suggest that these women and their fetuses may benefit from weekly fetal surveillance. Two thirds of the members of the Society of Perinatal Obstetricians use some form of fetal surveillance in uncomplicated gestational diabetes. More frequent testing is indicated in diet-controlled patients in whom pregnancy-induced hypertension or the need for insulin therapy develops or who have a history of stillbirth.

Delivery is indicated when the maternal or fetal condition deteriorates. These situations include the development of

pregnancy-induced hypertension or a history of decreased fetal movement supported by persistently poor fetal testing over one to two days. Pregnancy should rarely be carried beyond 40 weeks except in women well controlled by diet with no other risk factors. In such situations, fetal surveillance should be used until cervical ripening or 42 weeks of gestation. Elective interventions, such as a cesarean section at 38 weeks or inductions of labor, should be preceded by evidence of fetal lung maturity.

The long-term morbidity of gestational diabetes includes type II or non–insulin-dependent diabetes mellitus. This disorder in turn is associated with a higher frequency of end-organ failure, such as kidneys, eyes, and heart, especially in minority populations. Continued attention to diet, weight control, and exercise may reduce these risks.

At eight weeks postpartum, women with gestational diabetes mellitus should be tested with a standard 75-gram, two-hour glucose tolerance test. Women with abnormal test results should be seen by a diabetologist.

Although the risk of congenital anomalies is not reduced by diagnosing diabetes during pregnancy, this approach identifies a population that should undergo preconception counseling. Such counseling begins before the next pregnancy, which should be planned. It encourages women at risk for gestational diabetes to begin good glucose control two to three cycles before a planned pregnancy. This approach is associated with a substantial reduction in congenital anomalies.

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RU 486 (Mifepristone)

RECENTLY APPROVED for use as an abortifacient in the United Kingdom and in France, RU 486 (mifepristone) is the first of a new class of antiprogestins. When given in early pregnancy, it saturates progesterone receptors in the endometrium but does not act as an agonist. Progesterone is essential to sustain an early pregnancy, and if its action is blocked by RU 486, an abortion ensues. When given in a single oral dose of 600 mg before seven weeks' gestation, abortion rates of 80% to 90% can be achieved. If the dose of RU 486 is followed in 36 to 48 hours by a small dose of prostaglandin, the efficacy increases to more than 90%. The prostaglandin can be given as an intramuscular injection, a vaginal suppository, or orally by tablet. In the largest series of such abortions reported from France, the abortion rate was 96%. Morbidity rates have been low, although heavy bleeding can require curettage for management.

RU 486 may have a broad range of uses in reproductive medicine. When given to both pregnant and nonpregnant women, it causes softening and dilation of the cervix. When given 24 hours before beginning a second-trimester abortion by labor induction, it can reduce the time required by more than 50%. Its usefulness for inducing labor at term remains to be studied. Experience with RU 486 as medical therapy for ectopic pregnancy has not been encouraging. One small study found that daily treatment of endometriosis with RU 486 for three months led to a relief of symptoms without objective lessening in the extent of disease.

RU 486 may have applications beyond reproductive medicine. For example, the drug might be useful in treating women with metastatic breast cancer resistant to current therapies. In a study of 22 women after menopause or oophorectomy with therapy-resistant metastatic breast cancer, 18% showed a response to the drug at three months. When given in doses larger than that required to block progesterone receptors, RU 486 also blocks glucocorticoid receptors; the drug has been shown to be useful in treating Cushing's syndrome. Studies of its use in treating glaucoma and meningioma are in progress.

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Management of Hirsutism

HIRSUTISM, or male-pattern hair growth in women, is a common cosmetic complaint. The differential diagnosis includes pathophysiologic processes that either increase androgen production (polycystic ovary syndrome, late-onset congenital adrenal hyperplasia, Cushing's syndrome, or neoplasm) or increase androgen activity at the hair follicle itself (increased 5α-reductase activity). Regardless of the cause, the presence of hirsutism implies a net hyperandrogenic effect at the hair follicle. Evaluation requires a careful physical examination and the measurement of serum androgens (testosterone and dehydroepiandrosterone). The physical examination should include areas of male-pattern hair growth such as the upper lip, chin, neck, midline chest, and lower abdomen. If serum androgen levels are elevated—testosterone greater than 1.8 nmol per liter, dehydroepiandrosterone greater than 9.5 μmol per liter—then disorders of androgen overproduction such as polycystic ovary syndrome or late-onset congenital adrenal hyperplasia should be considered. If serum androgen levels are normal, then increased 5α-reductase activity is diagnosed by exclusion. Once a diagnosis has been made, treatment can be considered. The cornerstones of medical treatment involve inhibiting adrenal or ovarian androgen production; altering androgen binding to sex hormone-binding globulin (SHBG); or blocking androgen receptors.

Ovarian androgen production can be suppressed in several ways. The use of combination estrogen-progestin (oral contraceptive) therapy lowers free testosterone levels by suppressing ovarian production of androgens and increasing SHBG. Because hirsutism is commonly associated with menstrual irregularities, oral contraceptives can also provide menstrual cycle control. Gonadotropin-releasing hormone agonists, such as leuprolide acetate or nafarelin acetate, have been used successfully to treat hirsutism by inhibiting ovarian androgen production. Because of the effects of estrogen deprivation, however, long-term treatment with these agents is not feasible.

Selective suppression of adrenal androgen production may be induced with low dosages of dexamethasone. This is

particularly effective in women with elevated adrenal androgen levels due to late-onset congenital adrenal hyperplasia. Dexamethasone is administered at night so that the early morning peak in adrenal secretory activity is suppressed. Therapy is started with 0.125 mg daily and can be increased to 0.25 mg if suppression is not achieved within three months.

The single most effective treatment of hirsutism involves the blockade of androgen receptors. Spironolactone is an androgen-receptor blocker that also inhibits 5α-reductase activity. Therefore, spironolactone can be used to treat hirsutism regardless of the cause and is frequently used in combination with an agent that suppresses androgen production. Patients generally start therapy with 100 mg daily and may increase to as much as 200 mg daily. The effectiveness of spironolactone is first seen at three months and is maintained thereafter.

It is important to emphasize to patients that improvement is often not seen for three to six months. Once pharmacologic therapy has been initiated, adjunctive local treatments such as depilatories, waxes, and electrolysis can be undertaken to accelerate the desired cosmetic changes. Because hair follicles need only brief exposure to androgens to initiate growth, long-term compliance with therapy is essential to maintain satisfactory results.

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Who Is a Candidate for Norplant?

LEVONORGESTREL-CONTAINING soft plastic (Silastic) implants are a new form of contraception that many patients are requesting. The product consists of six flexible Silastic capsules that are inserted into the subcutaneous tissue of the medial arm. An aseptic technique is required. Expulsion is rare except in cases of infection or if the capsule is placed less than 0.5 cm from the incision. Positioning the implants in a fan shape at the same tissue depth during insertion makes removal easier. Removal of the implants takes twice as long as insertion because a layer of scar tissue that forms around each capsule must be incised.

The method is extremely effective in preventing pregnancy. In multicenter trials involving almost 2,500 women, 0.2 pregnancies per 100 women occurred in the first year. The cumulative five-year pregnancy rate was influenced by body weight. Only 0.2 pregnancies were noted among women weighing less than 50 kg (110 lb) over the five-year study period. For women weighing 50 to 69 kg (110 to 153 lb), the cumulative five-year pregnancy rate was 3.4 to 5.0. The rate was 8.5 for women weighing more than 70 kg (154 lb) and was noticeably worse beginning in the third year of use. In lighter women, the rate of pregnancy prevention is comparable to that with female sterilization.

The acceptability studies done in four different countries showed that the perceived advantages of the method were similar in all four countries: foremost was the ease of use, followed by effectiveness, long duration, reversibility, and arm placement. The most frequent misconception about the method was that it caused cancer or sterility. Most women requesting Norplant assume that it will work like the oral contraceptive pill, and careful counseling is needed to explain the method and emphasize how it will differ from past methods of contraception. In an overseas study, the one-year continuation rate in women without effective counseling was 60% compared with 88% when more rigorous preinsertion counseling was provided.

The predominant side effect of the implants is a disruption of the menstrual cycle. Because abnormal bleeding is an anticipated side effect, a biopsy is not recommended—even in women older than 35 years with irregular bleeding—provided they had regular cycles before insertion. Women with no menstrual bleeding are tested for urinary human chorionic gonadotropin at four and six weeks. If these tests are negative, the patient is reassured that it is a normal response to the method. Amenorrhea of pregnancy is consistently preceded by a pattern of regular monthly bleeding caused by ovulatory cycles.

Abnormal bleeding patterns improve with extended use. Those women who initially experience scant bleeding report more bleeding in subsequent years, and those with initially increased bleeding tend to bleed less with continued use. Despite changes in bleeding patterns, decreases in hemoglobin or ferritin concentration are extremely rare in Norplant users. Few women anticipate the extent of these menstrual changes—especially the unpredictability of individual response—and careful counseling is required both before and during the early months of use to prevent an early discontinuation of the method.

Patients with impaired glucose tolerance or hyperlipidemia should be carefully monitored in the initial use of the product. It is possible that the levonorgestrel may worsen these conditions or reduce the response to treatment. Women with impaired liver function may metabolize the levonorgestrel poorly, and the progestin may cause fluid retention. The product may alter vision or lens tolerance in contact lens users. Many women have constant premenstrual symptoms, and patients with a history of depression may find that the capsules precipitate a recurrence. In cases where there is some question about whether the method would be tolerated, women can be placed on a course of levonorgestrel-only oral contraceptives for a short trial (with condoms for added protection) before placing the implants.

The ease of use of the continuous-release capsules makes the method ideally suited for women who have used oral contraceptives without side effects but who forget to take their medication on a regular basis. It is also ideal for women with contraindications to estrogen and those who have estrogenic side effects from oral contraceptives. Careful attention to counseling before placement and patient selection will enhance satisfaction with the method.

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Substance Abuse in Pregnancy

PREGNANCIES COMPLICATED by the use of substances with abuse potential occur at an alarming rate. A 1988 survey of 36 hospitals found that 11% of women having children in those hospitals had used an illegal drug at some time during pregnancy. In a population-based survey of 715 women entering prenatal care during six months in Pinellas County, Florida, 14.8% of the women had a positive urine toxicology screen for cocaine, marijuana, alcohol, or heroin. This prevalence was independent of racial and socioeconomic differences. These findings reflect the high rate of substance use among women of childbearing age (15 to 45 years). Within this group, 60% (34 million) are current drinkers, 32% (18 million) are smokers, and 11% (6 million) use marijuana. Women in this age group often alter their substance use when pregnancy is diagnosed. Fetal damage may already have occurred, however, because diagnosis frequently takes as long as two months. When women cannot alter their substance use during pregnancy, maternal and fetal health are even further compromised. The costs of these complicated pregnancies to mothers, children, families, the health care system, and society as a whole are high.

Nearly all physicians have an opportunity to affect this serious epidemic. Primary care physicians can take advantage of routine gynecologic examinations, prepregnancy visits, and other office visits to provide information and counseling regarding the effects of substance use. Specialists who care for women may actually be treating secondary effects of substance use. For example, substance abuse is associated with an increased number of emergency department visits related to accidents and violence. Substance users may present with respiratory or gastrointestinal complications or with complaints of physical pain or stress-related illnesses. Encounters in these settings may also offer valuable opportunities for counseling.

In the ambulatory setting, a screening interview should always be done, accompanied by urine toxicology screens when indicated. The screens may require informed consent, depending on regulations. The effectiveness of the screening interview is enhanced when done within the context of a functional physician-patient relationship. Such a relationship can be quickly established, in most settings, given most patients' inherent desire to trust their physician. This foundation can be built on by expressing empathy, respect, and a desire to work with the patient toward achieving the best result. The subject of substance use or abuse is best addressed when discussing nutrition, exercise, and other patient-controlled health issues. The discussion should begin with prescription drugs and proceed through nonprescription drugs, caffeine, tobacco, alcohol, and illicit drugs. If the use of any substance needs further evaluation, the CAGE questionnaire for alcohol and other drugs or, for alcohol in pregnancy, the T-ACE questionnaire is especially useful.

When substance use is discovered, the presentation of the diagnosis is important. The physician should provide facts about substance use and its effects ("scare tactics" can be extremely counterproductive) and explain the possible consequences of continued use. Any link between signs and symptoms noted and substance abuse should be explicitly stated. Allow the patient to describe her understanding of the problems and check her understanding of the information provided. Next, either a definite treatment plan or a referral should be made. If both the patient and the primary care physician agree that the substance use problem may be amenable to treatment, a treatment contract may be indicated. This requires both parties to develop and agree on a plan for decreasing or stopping the use of the substance of concern. The patient should agree to this plan in writing, and a follow-up appointment should be made. When referral to a specialist is necessary, making the process of compliance easy for the patient helps referral to be more effective.

Substance abuse problems associated with prescription drugs are not rare among women. These problems can be reduced with extra care when prescribing potentially addictive drugs. Assessment should be made of any personal and family history of current and past drug use. The physician should consider the risk for drug abuse interaction with other drugs or cross-tolerance. The prescription should be on a fixed schedule, in small quantities, and for short periods of time. The patient should be reevaluated at frequent intervals, and prescriptions should be alteration-proof. Finally, the physician should assess the patient for pregnancy status, counsel the patient regarding possible effects of the medications in pregnancy, and offer information or referral regarding contraception or obstetric care.

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New Oral Contraceptive Progestogens

THE INTRODUCTION OF gestodene and desogestrel into the oral contraception pharmacopeia marks the first major change in many years. These high-potency 19-nortestosterone progestogens offer substantial benefits and high efficacy in both the monophasic and triphasic forms combined with ethinyl estradiol in the familiar 21- or 28-day cycle pattern.

Gestodene has 100% bioavailability, whereas desogestrel has 80% as it metabolizes to its active form, 3-keto-desogestrel. They are related to levonorgestrel but have virtually no androgenicity and no estrogenic effects. Furthermore, they have no effect on glucose metabolism, which enhances their value for patients at risk for diabetes mellitus. A unique property of gestodene is the effect of binding to aldosterone receptors. This may displace aldosterone from mineralocorticoids and may result in a lowering of blood pressure in some hypertensive patients.

A slight elevation of total blood cholesterol levels may be induced, but this occurs through the beneficial elevation of high-density lipoproteins and a reduction of low-density lipoproteins. An increase in triglycerides has also been reported. The overall effects of gestodene-containing oral contraceptives on lipids and lipoproteins are not clinically significant, however.

Clinical trials and extensive European experience indicate a decreased incidence of intermenstrual bleeding and amenorrhea when compared with the use of currently available oral contraceptives. This superior cycle control enhances

patient compliance. Women who abandoned the use of these oral contraceptives in clinical trials primarily cited weight gain or headaches as an undesired effect. As with other available birth control pills, nausea and mood changes were also cited. A risk of breast cancer in oral contraceptive users remains inconclusive and a source of patients' concern. There is some tentative evidence that gestodene mimics the effects of tamoxifen and therefore may actually reduce the risks of both breast cancer and benign breast disease.

With efficacy matching other available products, the new oral contraceptives offer enhanced patient compliance through the reduction of undesired breakthrough bleeding and amenorrhea. Their metabolic neutrality offers safety that equals or possibly surpasses that of other available contraceptives. Thus, they provide a good first choice for patients and an alternative for women experiencing problems with currently available oral contraceptives. Patients doing well on current formulations should not switch without indication.

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Premenstrual Syndrome

PREMENSTRUAL PHYSICAL and emotional changes occur in as many as 80% of women of reproductive age. The most common symptoms include fatigue, depression, irritability, breast tenderness, swelling, and food cravings. Estimates regarding the prevalence of the premenstrual syndrome (PMS) generally agree that 20% to 40% of these women experience some difficulty as a result of these changes during the premenstrual time interval, and 2.5% to 5% report a notable effect on work or life-style.

The diagnosis of PMS depends on the exclusion of other coexisting medical disorders. Although its incidence in the general population is high, most women do not have this condition as a chief complaint. Of those who do present with PMS, coexisting medical and psychiatric disorders are observed with startling frequency. The most important aid to clinicians in the diagnosis of PMS is the use of a monthly symptom rating inventory. Such inventories should reveal a relatively symptom-free interval from cycle day 4 through cycle day 12 and at least a 30% higher symptoms score in the late luteal phase (last seven days of the cycle) as compared with the midfollicular phase (cycle days 3 through 9). At least 25% of women having PMS-like symptoms will have no such symptom-free interval, suggesting the need for further medical and psychiatric evaluation, particularly for affective disorder, panic disorder, and personality disorder. An ultrasensitive thyrotropin level should also be obtained to screen for thyroid disorder. The incidence of perimenopausal symptoms is also high in this population, and a serum follicle-stimulating hormone level may be helpful in establishing the latter diagnosis. A substantial number of women have PMS symptoms while taking oral contraceptives. In these women, the oral contraceptive drug should be discontinued and symptoms prospectively evaluated while they use barrier contraception.

In a substantial number of women, symptoms are not adequately controlled by exercise, the elimination of caffeine and chocolate, and diuretic therapy. Recent evidence provides strong support for the hypothesis that progesterone modulates central neurotransmitter activity within the opioidergic, serotonergic, and γ-aminobutyric acid (GABA)-ergic systems. The currently accepted hypothesis of PMS is that progesterone acting through these central neurotransmitter alterations causes the behavioral symptoms of PMS. At present, although there is no safe way to intervene directly into the opioidergic system, double-blind placebo-controlled studies have shown a pronounced reduction of PMS symptoms using the serotonin uptake inhibitor, fluoxetine hydrochloride, at a dose of 20 mg daily throughout the menstrual cycle. Similarly, several double-blind studies have shown marked benefit using alprazolam, a benzodiazepine that acts on the GABA-receptor complex, in doses of 0.25 mg four times a day during the last week of the menstrual cycle. The addiction potential of alprazolam mandates that it be reserved for reliable patients and restricted to the latter part of the menstrual cycle. Nonetheless, these therapies provide the first conclusively proven beneficial therapy for PMS.

At least three studies have shown the efficacy of long-acting gonadotropin-releasing hormone agonists in premenstrual syndrome. Until the problems of resultant osteoporosis are overcome, however, this agent must be limited to short-term use.

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Therapeutic Options for Ectopic Pregnancy

THE ABILITY to detect ectopic pregnancies early with the aid of sensitive β-human chorionic gonadotropin (β-HCG) assays and intravaginal sonography has increased the options for treatment. Whereas exploratory laparotomy was once the standard, laparoscopic management and medical therapy are now used more frequently.

The goals of both laparoscopic and medical therapy are to treat before substantial tubal destruction has occurred and to eliminate the increased risk, discomfort, and longer hospital stays associated with laparotomy. With the use of intravaginal sonography, an intrauterine pregnancy should be detectable in a patient with a β-HCG value of 1,000 to 2,000 IU per liter (International Reference Preparation standard) or greater. The exact value for this "discriminatory zone" will be a function of the reference standard being used, the resolution of the ultrasound equipment, and the skill of the ultrasonographer. Serial values of β-HCG may be followed both to look for an appropriate rise of greater than 66% every 48 hours, suggesting a viable intrauterine pregnancy, and to reach the "discriminatory zone."

When an intrauterine pregnancy is excluded, laparoscopy can then be done to both diagnose and treat the ectopic pregnancy. A linear salpingostomy, segmental resection, or salpingectomy can be done safely through a laparoscope de-

pending on the size of the pregnancy, the patient's desire for future fertility, and the ability to control hemostasis. Laparoscopic therapy will generally require a primary infraumbilical incision for the laparoscope and two or more smaller incisions in the suprapubic region for ancillary trocars. The outcome of subsequent pregnancies for women treated laparoscopically for the ectopic pregnancies is similar to that achieved by traditional exploratory laparotomy. There is a persistence rate of about 5% with laparoscopic salpingostomy, so these patients must be observed postoperatively with serial β-HCG measurements.

Medical therapy with methotrexate may be used first or to treat patients with persistently elevated β-HCG values after laparoscopic salpingostomy. One regimen is to give methotrexate, 1.0 mg per kg, and leucovorin calcium (citrovorum factor), 0.1 mg per kg, on alternating days until the β-HCG values decrease by 15% on two consecutive days. A maximum of four doses can be used consecutively. Criteria for medical therapy include hemodynamic stability, the absence of hepatic or renal disease, certain diagnosis (when a nonviable intrauterine pregnancy has been ruled out), and an adnexal mass measuring less than 3.5 cm sonographically in its greatest dimension. These patients should be counseled and observed closely with β-HCG values and liver function tests because about 4% will have tubal rupture and require surgical management. Results as measured by the patency of fallopian tubes by hysterosalpingogram and by subsequent pregnancy seem to compare favorably with surgical management.

Laparoscopic therapy and medical therapy for ectopic pregnancy are important advances because of their favorable patient acceptance and the potential effect on the economics of health care.

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Genetic Predisposition to Ovarian Cancer

OVARIAN CANCER remains the most common cause of death from gynecologic malignancy in developed countries. It was estimated that in 1991 20,700 new cases and about 13,000 deaths would occur in the United States alone. The "lifetime risk" of ovarian cancer developing in a woman in the United States is about 1.4%, with the vast majority of tumors (85% to 90%) being epithelial in origin.

Although the cause of ovarian carcinoma remains unclear, genetic susceptibility is an important risk factor. Pedigree analysis has revealed three distinct patterns of familial transmission involving epithelial ovarian cancer. The most common syndrome is site-specific, and the heritable risk is limited to cancer of the ovary. The second is often referred to as the breast-ovarian carcinoma syndrome, and women in these families are at increased risk for one or both cancers developing. The cancer family syndrome also involves ovarian cancer in association with endometrial, breast, and colon carcinomas.

The pattern of transmission for each is autosomal dominant with variable penetrance. Women with two or more first-degree relatives with ovarian carcinoma have as much as a 50% risk of becoming affected. An important factor is that in the first two syndromes, men may be carriers of the gene and can transmit it to half of their offspring. In the cancer family syndrome (Lynch syndrome II), men are also at risk for adenocarcinomas, especially colorectal, and transmit the deleterious gene to half of their daughters and sons. It is currently impossible to quantitate the risk in a woman with one first-degree relative or second-degree relatives who have ovarian cancer, although it is safe to say that it is greater than that in the population as a whole. Careful surveillance should begin in women in their early 20s.

The genetics of ovarian carcinoma have not been well described. A loss of alleles on chromosomes 1, 3, 6, 11, and 17 has been detected, which may represent the deletion of tumor-suppressor genes. The amplification of several proto-oncogenes has also been described.

Many physicians advise prophylactic oophorectomy for women at risk for familial ovarian cancer. The age of onset is significantly lower in patients with hereditary ovarian carcinoma, and, this being the case, oophorectomy is often done as soon as childbearing is completed. It has been recommended that routine pelvic examinations be expanded to include annual pelvic ultrasonography and the assessment of serum CA 125 levels starting at age 25 for women in this high-risk group. Unfortunately, oophorectomy does not offer complete protection. Adenocarcinoma of the mesothelium, which is histologically indistinguishable from ovarian cancer, has occurred in several patients.

Genetic risk factors account for only a small proportion of all patients with cancer of the ovaries, with estimates as high as 10% but more likely 3% to 5%. Still, this group represents a population that is important in terms of surveillance, prevention, and as an opportunity to further our understanding of this disease.

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Ovarian Cancer Screening

SCREENING FOR ovarian cancer has begun to receive a great deal of publicity both within the areas of clinical research and in the news media. This is undoubtedly due in part to the tragic and well-publicized deaths of young women with advanced disease; it is also likely caused by the frustration of dealing with a cancer that will strike more than 20,000 women annually, leaving about 13,000 dead. Because these cancers are detected in later stages, those afflicted have only a 13% to 20% chance of surviving five years. The early detection of other cancers has increased survival. Recommendations for ovarian cancer screening are aimed at detecting ovarian cancer at earlier stages in hopes of prolonging survival.

Tools now widely available for screening include the biochemical marker, CA 125, and ultrasonography. CA 125 represents an antigen to the coelomic epithelial derivatives and is measured in the serum using a monoclonal antibody. Its greatest use thus far is in the management of ovarian cancer patients with respect to regression or progression of

known disease. Unfortunately, elevated CA 125 levels are also seen in early pregnancy, endometriosis, pancreatitis, peritonitis, ascites, menstruation, fibroids, and pelvic inflammatory disease among other benign conditions, which limits its usefulness in screening for early ovarian cancers.

Ultrasonographers have developed strict criteria for describing pelvic masses likely to be malignant. Such sonographic criteria include ovarian echogenicity, an irregular contour, and a volume greater than 20 ml. They admit that these sonographic criteria cannot distinguish between early malignant and benign conditions. False-positive studies can lead to unnecessary or inappropriate surgical procedures with their attendant morbidity or even mortality. Even in combination with an abnormal CA 125 serum study and abnormal findings on a pelvic examination, the detection rate of ovarian malignancy with ultrasonography is not 100%.

A new diagnostic technique, transvaginal color Doppler ultrasonography, has shown some promise in identifying dynamic characteristics of normal versus neoplastic ovaries. Color Doppler quantifies the flow in these low-resistance vessels using a calculated "resistance index." A resistance index of less than 0.40 is considered abnormal. More studies are needed to determine the effectiveness of this technique alone or in combination with other diagnostic methods.

Ultimately the cost-effectiveness of ovarian cancer screening will need to address the number of surgical procedures that will be done to confirm the diagnosis. For the time being, no single test or combination of tests has been shown to be an effective predictor of early stage disease. Except for the high-risk population of women with first-degree relatives with a confirmed diagnosis of ovarian cancer, there appears to be no suitable test or combination of tests to warrant the routine screening of healthy, asymptomatic women for ovarian cancer.

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Alerts, Notices, and Case Reports

Secondary Syphilis Presenting as Nephrotic Syndrome

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NEPHROTIC SYNDROME is characterized by an increase in glomerular capillary permeability to proteins, especially albumin, which ultimately leads to sufficient proteinuria to exceed hepatic synthetic replacement capacity. The resultant hypoalbuminemia and corresponding hypo-oncotic pressure lead to generalized edema formation.

The usual causes of the nephrotic syndrome include nonimmunologic glomerular damage, such as from diabetes mellitus and amyloidosis, and immunologic damage to glomeruli from such diseases as systemic lupus erythematosus, occult malignancy (including hematologic and solid tumors), medications (especially gold and penicillamine), primary renal glomerulonephropathies (minimal change disease, focal glomerulosclerosis, membranous nephropathy, and rapidly progressive glomerulonephropathy), and some infectious diseases, such as malaria and subacute bacterial endocarditis. Immune complexes within the glomeruli, identified by immunofluorescence, are characteristic of these disorders. In a recent review of manifestations of secondary syphilis in 854 patients, the nephrotic syndrome was not noted in any patient.[1] Because of the rarity of nephrotic syndrome from secondary or latent syphilis and the uncertainty of its clinical course with antisyphilitic therapy, we report a case of the acute onset of nephrotic syndrome in a middle-aged man whose clinical course and serologic status were observed closely for a year after treatment with penicillin.

Report of a Case

The patient, a 53-year-old man, was seen one week after he had developed generalized edema and a mildly pruritic maculopapular rash involving his trunk, face, arms, and palms beginning several days after what he thought was an upper respiratory tract viral syndrome. The edema formation was associated with a 9-kg (20-lb) weight gain during the same brief period. Other than increasing fatigue, he had no other complaints.

He had a 20-year history of diabetes mellitus. His blood glucose levels had been well controlled on insulin therapy with near-normal hemoglobin A_{1c} levels as well. Before this admission to hospital, he had recent normal blood urea nitrogen and creatinine levels although proteinuria (2+) was noted on a routine urinalysis two years previously. No quantification of his proteinuria was done at that time. He was unmarried, heterosexual, and said he had had no sexual encounters for at least three years before this illness. Before that, he claimed to have been monogamous sexually with his ex-wife.

On physical examination, his blood pressure was 154/70 mm of mercury with otherwise normal vital signs. He had obvious anasarca and a maculopapular, pink rash of well-demarcated spots about 5 to 10 mm in diameter covering his trunk, arms, and face and slightly involving his palms. There were no oral or genital lesions. His examination otherwise revealed no abnormalities, and he had no funduscopic change of diabetes or other end-organ stigmata of long-standing diabetes.

Pertinent laboratory data included a hematocrit of 0.39 (39%) and a hemoglobin level of 130 grams per liter (13.0 grams per dl). A leukocyte count was 7.9×10^9 per liter (7,900 per μl) with a normal differential. A blood urea nitrogen level was 4.3 mmol per liter (12 mg per dl), and a creatinine level was 80 μmol per liter (0.9 mg per dl). His serum albumin level was 20 grams per liter (2.0 grams per dl). Microscopic analysis of a urine specimen revealed an inactive sediment. On a 24-hour urine collection, he had 12.3 grams of protein with a normal creatinine clearance. A VDRL test was positive at 1:256. A fluorescent treponemal antibody (FTA) test was also strongly positive. Antinuclear antibodies were not found. A serum complement 3 level was 0.51 grams per liter (51 mg per dl) (normal 0.55 to 1.20). Human immunodeficiency virus antibody testing was negative. A skin biopsy of his rash revealed a heavy lymphohistiocytic perivascular inflammatory reaction, especially prominent in the superficial dermis but also to a lesser degree in the deeper dermis as well. This was reported as consistent with secondary syphilis.

The patient's acute clinical onset of nephrotic syndrome in association with his rash, skin biopsy histopathologic findings, and strongly positive VDRL and FTA was felt to represent classic secondary syphilis complicated by nephrotic syndrome, despite his persistent denials of risk factors for acquiring it. Although diabetic nephropathy was considered as a possible cause, because of the temporal relationship between the occurrence of classic manifestations of secondary syphilis and the acute onset of the nephrotic syndrome in this patient with serologic confirmation of syphilis, a renal biopsy was not considered justified, pending his response to antisyphilitic treatment, because other potentially reversible causes of the nephrotic syndrome were not found. He was treated with penicillin G benzathine, 2.4 million units intramuscularly, for secondary syphilis and furosemide, 40 mg per day, for his edema.

Three weeks later, his edema had resolved and he had minimal residual rash. The furosemide therapy was discontinued. Within another two weeks, his rash had disappeared, and he remained free of edema. His VDRL titer at that time had diminished to 1:64. A second dose of penicillin was given. Three months after treatment with penicillin was initiated, a 24-hour urine specimen showed a pronounced reduction in the urine protein level to 0.8 grams per 24 hours with a rise in the serum albumin level to 38 grams per liter. Five months after he received penicillin, his VDRL reacted only at a 1:1 dilution. Again, the temporal correlation of his clinical and serologic manifestations of secondary syphilis and

(Magarian GJ, Marr C: Secondary syphilis presenting as nephrotic syndrome. West J Med 1992 Jun; 156:654-655)

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response to treatment were felt to confirm the etiologic association between secondary syphilis and nephrotic syndrome and to exclude diabetic nephropathy as the cause of his nephrotic syndrome.

A year after the diagnosis of nephrotic syndrome from secondary syphilis was made, he continued to be free of edema. A lumbar puncture was done a year later to exclude neurosyphilis. Cerebrospinal fluid chemistry measurements and cell counts were normal, and the VDRL was negative.

Discussion

From 1981 to 1989, the incidence of primary and secondary syphilis increased 34% in the United States.[2] This increase has occurred since the mid-1980s and is a result of the remarkable increase in the incidence of syphilis among African Americans. Syphilis continues to be the great mimicker of diseases. Many of its later manifestations are related to immune complex formation with tissue deposition.[3-9] There are few reports of renal involvement from secondary or latent syphilis in the past two decades in the English-language literature.[7-14] In the cases in which biopsies were obtained, an immune complex glomerulonephritis has been identified.[7-10,14] Microscopic studies of renal biopsy specimens have most often revealed a membranous glomerulonephritis,[3,4,7,14] but minimal change[8,13] and proliferative glomerulonephritis[9] have also been identified. Antitreponemal antibody has been eluted from renal glomerular deposits obtained by biopsy.[3,9]

Together these case studies support an immune complex origin for the nephrotic syndrome associated with secondary or latent syphilis.[3-14] Fortunately, this nephrotic state is short-lived with appropriate antisyphilitic treatment. In our patient and the several others with reported follow-up, the nephrotic state appears to last from a week[8] to several months after appropriate antimicrobial therapy has been administered.[14] With an increasing incidence of primary and secondary syphilis occurring since the mid-1980s,[2] syphilis must be considered in a patient with otherwise unexplained nephrotic syndrome. Because of the association of the acquired immunodeficiency syndrome with syphilis, syphilis should be considered when unexplained proteinuria and nephrotic syndrome occur in such patients.

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Seat Belt Use During Pregnancy

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MOTOR VEHICLE crashes are a major cause of death in women of childbearing age,[1] and a major proportion of all maternal deaths are caused by motor vehicle crashes.[2,3] It is well documented that the use of seat belts greatly reduces serious injury and death.[4-6] Several studies of pregnant women have shown improved survival of mothers and their fetuses when seat belts were worn at the time of motor vehicle crashes.[7,8] Although the use of seat belts has been mandated by state law in New Mexico since 1986, the percentage of pregnant women using seat belts is not known. Furthermore, little is known about attitudes and beliefs of pregnant women regarding the use of seat belts during pregnancy. The frequency of seat belt use and the factors influencing their use were investigated in women attending obstetric clinics affiliated with the University of New Mexico Department of Obstetrics and Gynecology.

Patients and Methods

During April and May 1989, all pregnant women receiving prenatal care through the University of New Mexico Hospital and its affiliated community clinics were asked to complete a questionnaire. All questionnaires were in English. Non-English–speaking patients, who make up about 5% of the clinic population, did not complete the questionnaire. The sample we analyzed thus represents a convenience sample of English-speaking, English-reading gravid women. The questionnaire was designed to be self-administered to assess demographics, risk-taking behavior—previous motor vehicle crashes, substance abuse—trimester of the initiation of prenatal care, seat belt use before and during pregnancy, reasons for seat belt use or nonuse, and personal knowledge about the use of seat belts during pregnancy. Data were analyzed using SAS packages (Version 5, SAS Institute, Cary, North Carolina). Statistical significance was evaluated using the χ^2 test unless otherwise indicated.[9]

Results

A total of 207 questionnaires were received from the two hospitals and from the four community-based obstetrics clinics. The response rate was approximately 75%. Most respondents were young, married, Hispanic gravid women (Table

(Schiff M, Kasnic T, Reiff K, Pathak D: Seat belt use during pregnancy. West J Med 1992 Jun; 156:655-657)

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1). Most completed the questionnaire during their second (34%) or third (56%) trimester of pregnancy.

Because neglecting to wear a seat belt can be considered a form of risk taking, the study population was questioned about other risk-taking behaviors. The use of tobacco, alcohol, and illicit drugs before and during pregnancy is summarized in Table 2. There was no relationship between risk-taking behavior and seat belt use before or during pregnancy.

TABLE 1.—*Demographic Characteristics of Women Completing Seat Belt Questionnaire (n=207)*

Characteristic	*%*	*Characteristic*	*%*
Mean age 24 yr		**Educational level**	
Range 14-42 yr		8th grade	3
Marital status		9th-11th grade	33
Single	39	High school graduate	37
Married	46	Some college/tech	20
Separated	4	College graduate	7
Divorced	11	**Monthly income**	
Ethnic background		<$250	20
Hispanic	60	$250-500	24
Non-Hispanic white	32	$501-750	26
African American	5	$751-1,000	22
Native American	1	$1,000+	8
Other	2		

TABLE 2.—*Substance Abuse Before and During Pregnancy, Seat Belt Questionnaire (n=207)*

Substance	*Before Pregnancy, %*	*During Pregnancy, %*	*Significance, P*
Tobacco (>½ ppd)	31	13	<.005
Alcohol (>3 drinks/wk)	19	1	<.005
Illicit drug	15	2	<.005

ppd = packs/day smoked

Nearly half (49%) of the women had been in a motor vehicle crash in the past (seriousness of the crash was not specified); of these, 53% were not wearing a seat belt. The 47% who had worn a seat belt were also more likely to wear a seat belt during pregnancy ($P < .002$).

Figure 1 shows the frequency of seat belt use before and during pregnancy. A significantly higher proportion of women reported a more frequent use of seat belts during pregnancy than before pregnancy ($P < .0001$, paired Student's t test).

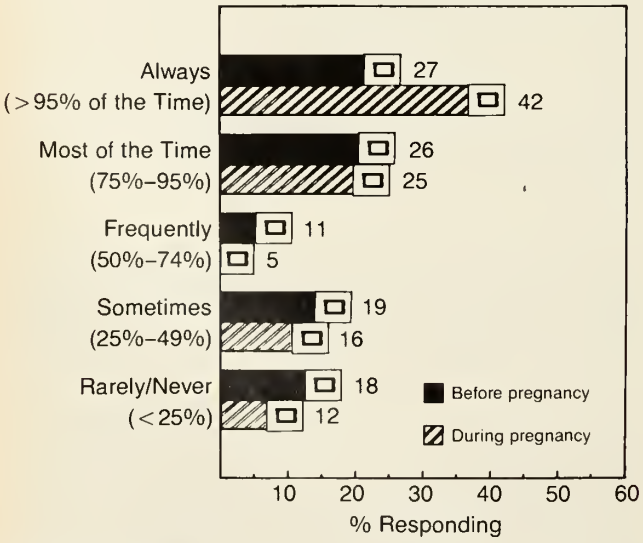

Figure 1.—The frequency of seat belt use before and during pregnancy is shown for 207 women.

The reasons women chose for wearing a seat belt during pregnancy are shown in Figure 2. Subjects wore seat belts to prevent injury to themselves or their fetuses. Many women reported wearing a seat belt to comply with state law. A wide variety of reasons were given for not wearing seat belts (Figure 3). More than half reported simply forgetting to wear a seat belt. Some stated the belt was uncomfortable to wear during pregnancy.

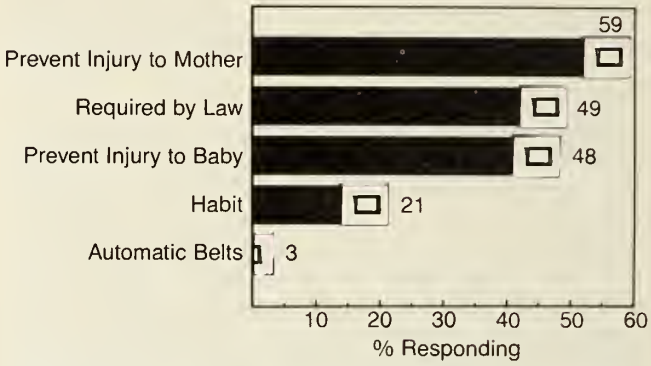

Figure 2.—Reasons for use of seat belts by 193 pregnant women are summarized (more than 1 answer was given by most women).

When the study population was divided into frequent (≥75% of the time) and infrequent (<75% of the time) seat belt wearers, the main reasons for the use of seat belts during pregnancy were different ($P < .0001$) (Table 3). Women who were frequent wearers were more likely to be motivated by the prevention of injury to themselves and by habit, whereas those who were infrequent wearers were more likely to be motivated by the law.

TABLE 3.—*Main Reason for Seat Belt Use Among Frequent Versus Infrequent Seat Belt Wearers*

	*Frequent Seat Belt Wearer**		*Infrequent Seat Belt Wearer†*	
Main Reason	*No.*	*(%)*	*No.*	*(%)*
Prevent injury to self	36	(38)	7	(17)
Prevent injury to baby	23	(24)	8	(20)
Habit	14	(15)	0	(0)
Required by law	21	(22)	25	(61)
Other	2	(1)	1	(2)
Total	96	(100)	41	(100)

*≥75% of the time. †<75% of the time.

Only 16% of the women had received any information about the use of seat belts during pregnancy. Almost a third (30%) of our sample were uncertain about the safety of seat belts during pregnancy, and 26% did not know the correct way to position a seat belt while pregnant.

Discussion

Motor vehicle crashes as a cause of maternal morbidity and mortality are a serious public health problem. Thus, the prevention of such morbidity and mortality through the use of seat belts during pregnancy should be an important public health goal. In New Mexico motor vehicle fatalities are

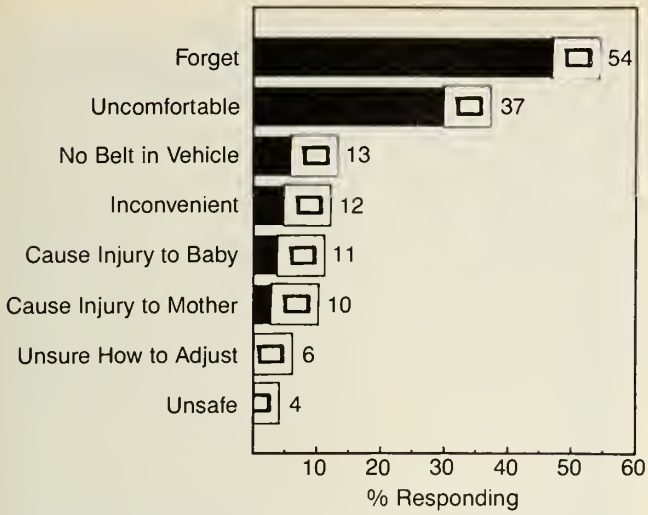

Figure 3.—Reasons for the non-use of seat belts by 145 pregnant women are summarized (more than 1 answer was given by most women).

nearly twice the national average.[1] More than half of our subjects had already experienced a motor vehicle crash. Thus, pregnant patients are at risk of injury or death from motor vehicle crashes.

Studies investigating the use of seat belts during pregnancy have shown a range of use from 32% to 90%.[10,11] This reflects not only use of seat belts but also seat belt laws and their enforcement as well as bias in reporting by subjects. Only one study made direct observations of pregnant patients in a parking lot of a prenatal clinic.[12]

Few studies have investigated changes in the use of seat belts prompted by pregnancy. Arneson and associates[10] found an increased use of seat belts during pregnancy in a retrospective study of postpartum patients. Our study population also increased the use of seat belts significantly during pregnancy when compared with use before pregnancy. The reason for this increased use was not addressed, although the change may reflect the women's overall decrease in risk-taking behavior—tobacco, alcohol, and drug use—during pregnancy.

The reasons for using seat belts during pregnancy focus on safety as well as legal issues. Our study confirms other reports[10,11] that showed that women use seat belts during pregnancy to protect themselves and their fetuses from injury. In the general population,[13,14] a law mandating the use of seat belts is the single most influential factor in increasing use. This is true for pregnant women as well, because a significant proportion of our subjects chose the law as a reason for wearing a seat belt during pregnancy.

Even with an overall increase in the use of seat belts, a significant proportion of our subjects were infrequent wearers. Attico and co-workers[15] conducted a seat belt promotion campaign in prenatal clinics in the Phoenix Area Indian Health Service. Pregnant women were given dashboard stickers to help remind them to buckle up. Although physical reminders help patients to remember to wear seat belts, the issues of correct positioning and uncertainty about the safety of seat belts during pregnancy emphasize the need to educate patients. Educators should remind patients that a proper use of seat belts during pregnancy involves placing the lap-belt portion under the abdomen and across the upper thighs, and the shoulder belt should cross the shoulder without chafing the neck and be positioned between the breasts.

Chang and associates[12] documented an increase in the use of seat belts after prenatal education classes that focused on seat belt use during pregnancy. Although the education of patients has proved effective, motor vehicle safety education programs are not routinely provided. Fewer than one of three obstetricians discuss the use of seat belts with their prenatal patients, and education material for patients about the use of seat belts is scarce in physicians' offices.[16]

Although there is a significant increase in the use of seat belts during pregnancy, a large proportion of pregnant women do not wear a seat belt consistently. To reduce maternal and fetal morbidity and mortality from motor vehicle crashes, education concerning motor vehicle safety during pregnancy must become an integral part of providing prenatal care.

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Reexpansion Pulmonary Edema in AIDS

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SPONTANEOUS PNEUMOTHORAX in association with *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome (AIDS) has been reported with increasing frequency. Reexpansion pulmonary edema is an unusual but well-described phenomenon that can occur with treatment of a pneumothorax. A case of reexpansion pulmonary edema after treatment of an AIDS-related pneumothorax is presented.

(Libraty DH: Reexpansion pulmonary edema in AIDS. West J Med 1992 Jun; 156:657-659)

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Report of a Case

Pneumocystis carinii pneumonia developed in a 32-year-old man with a three-year history of AIDS. His medications before diagnosis were β-carotene supplements and inhaled pentamidine, 300 mg per month. Pneumonia was diagnosed by examination of an induced sputum specimen. The patient was treated with oral trimethoprim-sulfamethoxazole—trimethoprim 320 mg, sulfamethoxazole 1,600 mg three times a day—for three weeks. Five weeks after diagnosis, the patient returned to the clinic because of mild dyspnea on exertion, pleuritic pain on the right side of the chest, and a temperature of 38.1 °C. Oxygen saturation was 94% on room air, and a roentgenogram of the chest revealed a 95% pneumothorax on the right side with no mediastinal shift (Figure 1). Initially he refused admission to the hospital but returned the following day for treatment.

Figure 1.—Spontaneous pneumothorax (95%) is apparent on the right side in a patient with a recent history of *Pneumocystis carinii* pneumonia and use of aerosolized pentamidine.

On admission a tube thoracostomy was executed, and the patient was placed on 20-cm water suction that resulted in immediate reexpansion of the right lung. Overnight, the patient became increasingly tachypneic and dyspneic, and rales developed on the right side. He remained hemodynamically stable, but his oxygenation worsened and required 15 liters of oxygen to maintain a saturation of 92%. A roentgenogram of the chest showed unilateral pulmonary edema on the right side (Figure 2). The patient was treated with supplemental oxygen and small amounts of morphine. Within two days, the symptoms and pulmonary edema resolved.

Discussion

Spontaneous pneumothorax in a patient with AIDS was first reported in 1984[1]; since then, it has been reported with increasing frequency. Sepkowitz and associates reported a series of 20 patients with AIDS-related pneumothorax.[2] They noted that the two risk factors for the development of pneumothorax were a history of aerosolized pentamidine use and of *P carinii* pneumonia. This patient had both, and his clinical course was complicated by reexpansion pulmonary edema.

Figure 2.—Unilateral pulmonary edema is present on the right side after reexpansion of the right lung via tube thoracostomy while receiving 20-cm water suction.

The phenomenon of reexpansion pulmonary edema was first described by Pinault in 1853 after removing 3 liters of pleural fluid from a patient.[3] The development of reexpansion pulmonary edema after evacuation of a pneumothorax was first noted in the modern literature by Ziskind and colleagues in 1965.[4] Over the ensuing years, several associated clinical factors have been reported: spontaneous, as opposed to traumatic, pneumothorax; lung collapse for more than three days; and the application of high negative intrapleural pressures.[5] Indeed, studies in animals have shown that these factors contribute to the formation of edema.[6]

The exact pathophysiologic process underlying reexpansion pulmonary edema remains unclear. In 1902, Riesman described a high protein content in reexpansion pulmonary edema fluid.[7] More recent studies reconfirmed the exudative nature of the fluid and demonstrated a unilateral increase in pulmonary microvascular permeability in the development of reexpansion pulmonary edema.[8,9]

Given the association of prolonged lung collapse and negative intrapleural pressures, the effects of tissue hypoxia or of mechanical disruption of the pulmonary capillaries, or both, have been considered to lead to the increased vascular permeability. Experimental evidence for these factors has been lacking, however.[10] More recent evidence points to reexpansion pulmonary edema as a form of reperfusion injury[5,10]: that is, the increase in microvascular permeability is related to the restoration of blood flow, the formation of oxygen-free radicals, the activation of neutrophils, and the generation of leukotriene and thromboxane.

Reexpansion pulmonary edema can lead to severe hypoxemia, hypotension, or, rarely, death. As the incidence of AIDS-related pneumothorax increases, so will the potential for reexpansion pulmonary edema as a complication of treatment. Patients who have a spontaneous pneumothorax and require tube thoracostomy for reexpansion should be connected initially to water seal only, because this will generally lead to an uncomplicated resolution of the pneumothorax. Those with prolonged lung collapse or who require negative intrapleural pressures for reexpansion

should be closely observed because of the possibility of the development of reexpansion pulmonary edema.

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Commentary

Drug Company Marketing in the Groves of Academe

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I have long maintained an interest in the interaction between the medical profession and the pharmaceutical industry, an interest focused by my participation in the University Group Diabetes Program (UGDP) and the attendant controversy.[1] So it has been easy to follow the mounting concern, here and abroad, about the corrosive effects of gift-giving by drug companies to practicing physicians.[2-5] The pressure for change, surfacing in articles in the lay press (M. S. Wilkes, M. Shuchman, "Pitching Doctors," *New York Times Magazine*, November 5, 1989, p 88) and in admonitory senate committee hearings, has culminated in the promulgation of guidelines.[6] The American College of Physicians has suggested a form of moral suasion: "A useful criterion in determining acceptable activities and relationships is: would you be willing to have the arrangements generally known?"[7] A more specific and less polite set of guidelines has been "issued as an opinion" by the American Medical Association (AMA) with the concurrent endorsement by the pharmaceutical industry.[8]

I see this turnabout as a triumph of sorts; a dangerous, corrupting trend has been condemned by both parties. It remains only to establish mechanisms to discipline the intransigent violators.

This satisfying state of affairs applies primarily to the expected behavior of the recipients of continuing medical education (CME); the role of medical academicians, the purveyors of CME, remains relatively unconstrained unless an offender strays beyond the regulatory bounds being set by the Food and Drug Administration.[9] Unlike the restrictions placed upon attendees, the AMA guidelines specifically permit "faculty (and consultants) to accept reasonable honoraria and to accept reimbursement for reasonable travel, lodging, and meal expenses."[8] Fair enough, but left untouched are any proscriptions against participating in CME activities that present views biased in favor of the sponsor. "In addition, when companies underwrite medical conferences or lectures *other than their own* (italics added), responsibility for and control over the selection of content, faculty, educational methods, and materials should belong to the organizers of the conferences or lectures."[8] An obvious corollary to this statement is that a company underwriting its own conference or lecture *may* control its content and faculty, leaving open the possibility that the content might be distorted by the selection of a faculty with either honestly held sympathetic views or with lamentably malleable ones.

The drug company-sponsored symposium is only one of a number of techniques used to promote pharmaceutical products. The pronouncements of a professorial circuit rider is another. Community physicians have become familiar with the visiting lecturer who extols, more or less subtly, the virtues of one drug while denigrating, more or less subtly, another. This lecturer may have been selected by the local CME director from a company-approved panel, a procedure that assures financial support for the director's program and a favorable hearing for the company. On a loftier scale, prestigious faculty may embark regularly on lucrative international lecture tours underwritten by not-disinterested pharmaceutical companies.

Medical academicians may choose to engage in other profitable activities. They may write for "throw-away" journals. They may construct lectures, complete with slides, for specialist practitioners to present to their colleagues. And, as members of higher academic echelons, they may be handsomely rewarded for presiding at a symposium, a favorite device for launching a new drug, medical device, or test procedure. In mounting such a symposium, the usual procedure is for a medically sophisticated drug company liaison officer to select a key academic figure to organize the program and select the speakers. The program does not often include the work of those who have reservations about the efficacy or safety of the featured drug. These sessions may be held immediately before or after a related national meeting, lending an aura of innocence by association.

The list of ethically questionable activities available to enterprising faculty goes on. A staff member at the Food and Drug Administration tells me that he marvels at the ease with which academicians, serving as drug company consultants, can refute their own previous testimony to fit changing circumstances. And a prominent academician enthusiastically endorses a drug company plan to reimburse elderly patients for the cost of any company product that "fails to achieve the desired therapeutic benefit."[10]

Clearly what has been emphasized here are distortions of otherwise healthy and synergistic interactions between medical academia and the pharmaceutical industry. Many drug companies behave well. They support CME activities regardless of a lecturer's message. There are faculty who reflexively shy away from any educational enterprise that might be perceived as biased. Nevertheless, situations arise that may perplex unwary academic souls whose hearts are pure. For them a simple caveat may be helpful: Do not agree to serve on a drug company panel. Though such a meeting may have all the accouterments of an academic endeavor, it comes off as an uneasy mix of a worthy CME activity and drug company hype, sometimes on an international scale.

How should we deal with these perplexing problems? What is needed is a hierarchy of nongovernmental oversight bodies to offer counsel regarding the acceptability of any

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proposed arrangement *before* it is consummated. Suitable guidelines should be promulgated, recognizing that they may not always suffice. As Havighurst has noted, "It is an irony of ethical canons that they discourage only the most conscientious and reputable physicians—the very least likely to abuse their trust—from embarking on questionable paths."[11] Indeed, disciplinary measures may be necessary. An errant faculty member should be admonished by a medical school ethics committee, and a complaisant university administration should be called to task by a peer group, such as the Association of American Medical Colleges.

My discussion has been confined to the role of academicians in CME, an activity that is only one component of the complex interrelations between universities and the pharmaceutical industry. Nevertheless, the effect of continuing medical education extends far beyond the dollars expended because CME deals directly with one of the core roles of the academician—teaching—and we must beware of the specter of the untrustworthy teacher.

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Last night I dreamt about you, she says to me.

You and I were moving. We planned to live
together. People told me it wouldn't
work out. I said we would make *it work out.*

Look what death does:
it smooths the way for God.

Later, as composition would have it
(each day now is made like a poem),
the visiting nurse has questions for me.

Where does your mother want to die?
Would she want us to resuscitate?
And if nutrition and water keep her alive,
after she enters a coma—would you want to taper off?

If death is the tool of God
and I am to be
a carpenter—

God—

guide my hand.

KAREN KESKINEN
Turlock, California

Commentary

Noninvasive Monitoring of Oxygenation and Ventilation
40 Years in Development

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In 1986 continuous monitoring of oxygenation with pulse oximetry and ventilation with the capnometer became a standard in operating rooms.[1] Over the next few years these devices have been applied in intensive care units as well. Although widespread use of these monitors did not begin until the 1980s, their development started 40 years earlier. It was clear that continuous noninvasive monitors that ensure oxygenation, ventilation, and perfusion would be extremely useful for critically ill patients, but it took about 40 years to overcome technical limitations in the design of these oximeters and capnometers.

Although many persons have contributed to the development of noninvasive oximetry, there are several who have made particularly significant contributions.[2] During World War II, Glen Alan Millikan was working on a method of assessing the oxygenation of pilots as they flew to higher elevations. The Germans were the first to institute compressed oxygen for high-altitude flying. It was important that we understood the effects of altitude on oxygenation and psychomotor performance. Millikan was the son of the Nobel Prize-winning physicist who was the cofounder of the California Institute of Technology in Pasadena. He realized from work completed in England and Europe that the intensity of light transmitted from transilluminated tissue changed with the oxygenation of the blood. He therefore developed an optical device, an "oximeter," that illuminated the tissues of the ear. The light source was placed on one side of the pinna and a detector on the other. He was hoping to determine the changes in arterial blood oxygenation by measuring the change of light absorbance by blood as it passed through the tissues. Unfortunately, the light was absorbed by multiple substances within the ear in addition to the blood. To eliminate the effect of light absorbance by the skin, cartilage, and other nonblood tissues, he first compressed the ear by inflating a cuff around the ear to eliminate the blood. He then used the light absorbance of this bloodless ear tissue as the 0 point. The cuff was deflated, allowing blood to return to the ear. A second problem was that not only arterial but venous and capillary blood contributed to the light absorbance. To eliminate this effect, he heated his device to 44°C, thereby arterializing all the blood beneath the device. He had the subject breathe oxygen to fully saturate the hemoglobin, producing a second calibration point of 100% saturation. The device would then follow changes in saturation with fair accuracy. Unfortunately, Millikan died in a mountain climbing accident at the age of 41.

After the war Millikan-type ear oximeters were used in physiologic research. A classic study was conducted by Comroe and Botelho in 1947.[3] These investigators tried to assess the ability of trained clinicians to detect cyanosis in humans. In all, 7,204 observations were made by medical students and medical staff while subjects breathed varying levels of inspired oxygen concentration. It was found that cyanosis could not be detected consistently until the saturation was below 80% and that multiple subjects were considered to be cyanotic at saturations in the 90s. This study concluded that even in a controlled setting, the clinical detection of cyanosis is extremely unreliable. It was also estimated that it requires about 5 grams of desaturated hemoglobin to produce cyanosis—that is, anemia makes cyanosis more difficult to detect. In 1951 an article appeared in which it was recommended that an oximeter would be useful on every anesthetized patient for it provided important continuous data regarding patient oxygenation.[4] It identified routine desaturation during normal anesthetic procedures in healthy patients. The authors also stated that there were many technical problems with the device, including the potential of burns to the ear. The clinical usefulness of the device was clear to the initial users 40 years ago.

In the 1970s, Hewlett-Packard developed an 8-wavelength ear oximeter that did not require calibration by squeezing blood from the ear and had improved accuracy due to its multiple wavelength technique. It did heat the ear to some extent but not to a temperature high enough to cause burns. This device became routinely used in pulmonary function laboratories. Also in the mid-1970s, an engineer named Takuo Aoyagi working for Nihon Kohden Corporation made an ingenious discovery. He was working on a noninvasive method to measure cardiac output by injecting dye in a peripheral vein and measuring the dye dilution curve noninvasively with an ear oximeter-like device. In the process of this work, he found that there was a pulsatile component to the absorbance detected by the ear oximeter. He noted that the amplitude of this pulsatile component changed with changing oxygenation. He surmised that the pulsatile absorbance was due to the pulsatile arterials and that it could be assumed that whatever was pulsing was arterial blood. Given that information, if only the pulsatile component of absorbance was analyzed, a signal related to arterial blood could be determined without heating the ear. He then developed the first "pulse" oximeter by analyzing the pulsatile component of absorbance in 2 wavelengths of light (red and infrared) and calibrated the ratio of these absorbances empirically to arterial saturation using human subjects. Although this device

(Tremper KK: Noninvasive monitoring of oxygenation and ventilation—40 years in development. West J Med 1992 Jun; 156:662-663)

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included all the theoretic aspects of the current-day pulse oximeter, it had considerable technical problems. The Nihon Kohden pulse oximeter used fiberoptic cables from the device to the ear to transmit the light signals. These cables were heavy, making it difficult to maintain the position on the ear. Its accuracy was also limited because of its simplified calibration process. In the late 1970s an engineer named Scott Wilbur in Boulder, Colorado, saw this device and decided to make an improved version. He used lightweight light-emitting diodes (LEDs) and photodiodes as light sources and light detectors. They could be made into an ear clip and placed directly on the ear. He also used a microprocessor to improve the empiric calibration and the accuracy of the device. His additions made the pulse oximeter a clinically usable device that was quickly adopted by pulmonary function laboratories. The final contributor to this developmental process was an anesthesiologist named Bill New. New was the faculty member at Stanford University who saw the pulse oximeter made by Wilbur and immediately realized its direct application to the operating room. He made an improved adhesive probe that included the photodiode and the LEDs. This Nellcor device quickly became a standard in operating rooms.

Today, if given the choice of one monitor, most anesthesiologists would quickly choose the pulse oximeter over the electrocardiogram (ECG) or noninvasive blood pressure devices. Its familiar beep that changes tone with saturation has become a reassuring sound for everyone in an operating room. In fact, if pulse oximeters had been developed before ECGs, it might be difficult to justify the purchase of ECGs for each operating room. Although the pulse oximeter does not detect perfusion changes per se, it will quickly detect the absence of a pulse.

Infrared CO_2 analyzers were also first developed during World War II. The original devices were used to measure CO_2 concentrations in German submarines. After the war this "Luft" analyzer became the standard device for CO_2 measurement. The absorbance of infrared light by carbon dioxide was used to determine the CO_2 concentration. Although there have been many improvements in the technical development of CO_2 analyzers over the past 40 years, the basic Beer's Law absorption theory on which the capnometer (and pulse oximeter, for that matter) is based is still the same. Its use in medicine was limited until the work of Smalhout and Kalenda in Holland.[5] They measured expired CO_2 waveforms from anesthetized patients and published an atlas of capnography. This atlas of their clinical experiences with the device demonstrated that it provided breath-to-breath assessment of ventilation and pulmonary perfusion. This was found to be so useful in assuring the stability of anesthetized patients that in Holland its use became routine by the end of the 1970s. In the United States capnography was only used in neuroanesthesia until appreciation for its usefulness gradually grew in the 1980s. By 1986 it was adopted as a routine monitor for all anesthetic procedures along with pulse oximetry.[1]

It is difficult to imagine caring for anesthetized patients in the 1990s without these two devices. Because surgical intensive care units are direct extensions of intraoperative care, it would seem only reasonable that critically ill patients receive similar monitoring. Because of its ease of interpretation, pulse oximetry has been quickly adopted in critical care units. Capnography requires more interpretation because it provides data that relate not only to ventilation but to pulmonary perfusion abnormalities.[6-8] For this reason, it took nearly half a decade for it to be appreciated in operating rooms and, most likely, will take several years of familiarity with it in intensive care units before it becomes routinely applied. These two noninvasive monitors of the cardiopulmonary system are extremely useful in all critical care settings, but users must have "an understanding of the underlying assumptions and limitations"[9] to employ them intelligently.

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Editorials

Practical Therapeutics in Patients With Renal Impairment

THE RELATIONSHIP between the amount of a drug in the body and the drug's effects has been recognized for almost 150 years.[1] In the middle of the 19th century, Buchanan appreciated that the brain content of the new anesthetic, ether, depended on the strength of the inhaled mixture and the arterial concentration of the compound. He calculated the amount of the anesthetic retained during induction and related it to the depth of narcosis.

Nearly a century later, Torsten Teorell, a Swedish physiologist, described the first physiologically based model of drug behavior.[2,3] In his view, drug disposition was accounted for by a five-compartment model that included renal elimination as one factor influencing the amount of a drug retained in the body. His model predicts that drugs eliminated by the kidneys would accumulate in patients with impaired renal function.

This projection was confirmed by Kunin and Finland in 1959 with their report of antibiotic accumulation in patients with renal failure.[4] During the next decade, investigations of many frequently used drugs documented the dependence of drug elimination on renal excretion.[5,6] The data on drug elimination in patients with impaired renal function remained limited and scattered through many specialty publications.

In 1970, Bennett and colleagues compiled the first extensive list of frequently used drugs in patients with renal impairment and provided practical guidelines for dosing at various levels of renal function.[7] Although this work included specific dosing recommendations for 72 drugs based on 78 references, scarcely three years passed before a supplement containing 69 additional drugs or changes and 130 references was required.[8]

The rapid proliferation of complex and effective new drugs has added to the challenge of rational drug therapy in patients with abnormal renal function. Nearly a third of the antibiotics currently prescribed were not available five years ago.[9,10] Selective agonists and antagonists of cell receptors and specific enzyme inhibitors are readily available, as are biosynthetic peptide hormones. Pharmacokinetic data in patients with decreased renal function are now available for more than 300 commonly prescribed drugs from over 600 reference sources.[10]

Adverse reactions to drugs occur three times more frequently in patients with impaired renal function.[11] Alterations in drug absorption, distribution, protein binding, metabolism, and excretion of drugs and metabolites seen in patients with renal impairment play an important role in the therapeutic or toxic response to a drug. These adverse responses are most likely the result of drug doses inappropriate for patients' level of renal function.

Since that first list, "the Bennett tables" containing specific dose recommendations for patients with impaired renal function have appeared every three to five years as journal articles, supplements to journals, and, most recently, in book form. They can be seen in the overly laden white coat pockets of many house-staff physicians and on the bookshelves of most hospital libraries. In intensive care and dialysis units, well-worn copies are usually labeled, "Do Not Remove From . . ." to avoid their inevitable disappearance into a coat pocket or black bag.

Because the kidneys are the major regulators of the internal fluid environment, clinicians must possess a basic understanding of the biochemical and physiologic effects of drugs in patients with renal disease. Elsewhere in this issue of the journal, Swan and Bennett present a concise overview of drug disposition in patients with impaired renal function.[12] They provide a rational basis for practical therapeutics and specific guidelines for drug dosing at all levels of renal function. The table presented in their review (Table 2) provides practitioners an updated starting point for the careful use of frequently prescribed medications in a population at risk for adverse drug effects.

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Autoimmune Disease and the Nervous System*

THE NERVOUS SYSTEM, once considered to be sequestered from normal immune surveillance, can be the target of an autoimmune attack. Myasthenia gravis has been proved unequivocally to be an autoimmune disease mediated by antibodies to the acetylcholine receptor (AChR).[1] The case for autoimmunity in the pathogenesis of multiple sclerosis, involving an inflammatory response in the white matter of the central nervous system, and the Guillain-Barré syndrome, involving an inflammatory response in the myelin sheath of peripheral nerve, is strong.

Myasthenia gravis, a disease characterized by fatigable

*This editorial accompanies "Autoimmune Disease and the Nervous System—Biochemical, Molecular, and Clinical Update" by J. Merrill, MD, M. Graves, MD, and D. Mulder, MD, pages 639-646 of this issue.

weakness of skeletal muscle, is perhaps the best understood of all the autoimmune conditions in humans. The disease is mediated by an antibody response to AChR that may have been triggered by a response to an infectious pathogen whose structure mimicked in part that of the AChR.[2] Among the molecules that mimic AChR is a peptide encoded by herpes simplex virus 1.[2] Thymic abnormalities including hyperplasia and thymoma are common. Indeed, the breakdown in self-tolerance for AChR may occur in the thymus. Primitive myoidlike cells bearing AChR are seen in normal thymus. Susceptibility to myasthenia gravis is associated with certain HLA genes, and the disease often occurs in conjunction with thyroiditis, insulin-dependent diabetes mellitus, and systemic lupus erythematosus.

The case for the role of anti-AChR antibody in the pathogenesis of the disease is irrefutable. Pregnant women with myasthenia gravis can passively transfer their disease to the fetus, although as maternal immunoglobulin (Ig) G levels decrease in the first trimester, the babies make a full recovery. Immunoglobulin G can be taken from a myasthenic person and transferred to mice with a full recapitulation of the clinical picture of fatigable weakness.[3] Immunizing laboratory animals with AChR leads to a disease resembling human myasthenia gravis in every way. Nearly 90% of patients with the disease have detectable antibody to AChR at some point in the course of their illness. It is known that the antibodies impair neuromuscular transmission by reducing the amount of AChR that is available for interaction with the neurotransmitter acetylcholine. Chronic myasthenia gravis can lead to an actual degradation of the exquisite ultrastructure of the neuromuscular junction.[3]

The treatment of myasthenia gravis involves the use of anticholinesterase drugs in conjunction with immune suppression. A major therapy for myasthenia gravis over the past 50 years has been total thymectomy. This is particularly useful in young patients, including children, in patients with early clinical manifestations of systemic disease, and particularly in women. In a recent review of a 32-year experience with thymectomy at the UCLA Medical Center involving 333 patients, 85% benefited from the operation. Total remission (no medication and no symptoms) was achieved in 50% of the women and 38% of the men. Improvement (less medication and fewer symptoms) was noted in an additional 37% of the women and 41% of the men.[4]

It is not clear how thymectomy aids patients who have myasthenia gravis. The thymus may be a critical site for the pathogenesis of the disease and for a breakdown in the physiologic positive and negative selection procedures that help maintain self-tolerance. Nearly 80% of patients have identifiable thymic disease, including lymphofollicular hyperplasia, and about 10% of patients have thymic neoplasia.[5] Melms and associates[5] hypothesized that in patients with myasthenia gravis the thymus is the primary site for the pathogenesis of the breakdown of tolerance to AChR. Indeed, myoid cells in the thymus synthesize and express AChR. Autoreactive T cells may then recognize AChR in the thymus and migrate to the periphery where they interact with B cells to produce anti-AChR antibody.[5] It has been shown that thymocytes obtained at thymectomy in these patients respond specifically to AChR even more vigorously than T cells taken from peripheral blood.[5,6]

In healthy states, immunologic tolerance to AChR is maintained. There are at least four ways whereby tolerance to a self-constituent like AChR is maintained.[7] First, unresponsiveness might be maintained if AChR or its fragments cannot bind to the major histocompatibility complex (MHC). Second, AChR-reactive thymocytes could be deleted from the T-cell repertoire by clonal deletion in the thymus. Third, unless muscle cells express MHC class II molecules or unless B cells that constitutively express MHC class II molecules bind AChR, AChR would not be immunogenic for T-helper cells. Myoblasts can be induced to express MHC class II by administering interferon gamma.[8] In addition, B cells could react with viral or bacterial pathogens with determinants that mimic AChR.[2] Fourth, T cells may suppress a response to AChR. A breakdown in these suppressor-cell circuits could activate a T-helper cell reactive to AChR.

Our understanding of the pathogenesis of the major demyelinative diseases of the central and peripheral nervous systems, multiple sclerosis and Guillain-Barré syndrome, respectively, lags far behind our knowledge of myasthenia gravis. Despite this situation, several major clues concerning the immunogenetics of these conditions point to the strong possibility that these diseases are autoimmune. It is important to note, however, that even in a degenerative condition like Duchenne muscular dystrophy, caused by a mutation in the gene encoding dystrophin, there is an inflammatory response at the site of disease, presumably directed against degenerating muscle tissue.[9] Even though Duchenne muscular dystrophy is not an autoimmune disease, there may be a pathogenic role for this immune response because immune suppression slows the progression of this lethal disease.[9] Thus, although multiple sclerosis is probably an autoimmune condition, the possibility exists that the primary trigger for the disease might in fact be a degenerative condition in white matter.

There is a strong foundation for a genetic basis for multiple sclerosis. Identical twins have a concordance rate for clinical multiple sclerosis of 26%, compared with 2.3% for dizygotic twins and 1.9% for nontwin siblings.[10] There are associations between susceptibility to multiple sclerosis and genes of the major histocompatibility complex, the T-cell receptor gene complex, and the immunoglobulin allotype.[11] Unfortunately, at the present time we do not know the major target antigens in multiple sclerosis, although a large body of evidence points to two major proteins of the myelin sheath, myelin basic protein and proteolipid protein. In nearly two thirds of patients with this disorder, antibodies to myelin basic protein can be detected in cerebrospinal fluid.[12] The T-cell clones reactive to myelin basic protein can be cultured from the peripheral blood of patients with multiple sclerosis at a much higher frequency than from that of healthy controls.[13,14]

With the conviction that multiple sclerosis is an autoimmune disease, new therapies are being developed that are aimed at targeting the components of a trimolecular complex involving the major histocompatibility complex, the T-cell receptor, and the myelin antigen. Earlier attempts with nonspecific immune suppression involving azathioprine, cyclophosphamide, and cyclosporine have not met with consistent success.[15] Modern treatments with peptides like copolymer 1 aimed at blocking the interaction of T-cell receptor with myelin basic protein bound to HLA molecules look promising.[16] Results of trials attempting to induce oral tolerance to myelin antigens and vaccinating against T-cell receptors reactive to myelin basic protein[15] will be reported

soon. As our understanding of the pathogenesis of multiple sclerosis increases, the new therapies for this disorder will become more precise, with the prospect of greater success and less toxicity.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Tic or Dystonia?

To THE EDITOR: Diaz and colleagues recently reported the case of a 19-year-old with a 15-year history of repetitive turning of the neck to the right side, which was diagnosed as chronic motor tics.[1] Haloperidol use exacerbated the neck turning and also precipitated new stereotypic buccal movements labeled tics. We wonder whether both types of abnormal movements might have been dystonias rather than tics. While there is a common perception that dystonias are fixed abnormal postures, they also may be repetitive patterned movements of variable speed.

The patient's neck turning to one side may have been torticollis, a cervical dystonia. Distinguishing torticollis from a simple tic of the neck depends on clinical features. Tics are typically rapid, unsustained, nonrhythmic, preceded by an urge to move, and strongly responsive to volitional suppression; not every one of these features need be present. Both tics and dystonia may be aggravated by mental stress.

The isolated buccal movements that arose during treatment with haloperidol may have represented an "extrapyramidal reaction." Two such neuroleptic-induced movement disorders are "rabbit syndrome" (a parkinsonian facial tremor) and acute neuroleptic-induced dystonia. Given the patient's youth, the onset within the first week of haloperidol therapy, and the tendency for acute drug-induced dyskinesias to affect the face, the second explanation might be more likely.

A detailed description of abnormal movements is prerequisite for diagnosing movement disorders. The distinction between tic and dystonia is important because the conditions have important differences in their treatment. Tics might be treated as the authors outlined; cervical dystonia is treated best with botulinum toxin injections, anticholinergic agents, or benzodiazepines.

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* * *

Dr Diaz, Mr Smith, and Dr Maccario Respond

To THE EDITOR: Drs Wasserstein and Honig's letter raises the possibility that our patient had an exacerbation of cervical dystonia and an induction of an acute neuroleptic syndrome after haloperidol therapy. Although this is a reasonable hypothesis, after we describe our patient's movement, it will be clear that he met all the diagnostic criteria for chronic motor tic.[1] His stereotypic neck movements, which are the second most common type of motor tic,[2] started at 4 years of age. The neck movements were sudden, rapid, recurrent, nonrhythmic, and involuntary. Our patient felt compelled to move his neck to the right. Although this movement could be voluntarily suppressed, a tension would develop if he resisted. Once he carried out the movement, the tension would be relieved. In contrast, cervical dystonia has a mean age of onset of 41.8 years (range, 9 to 74 years), is accompanied by a sensation of pulling or drawing, is sometimes painful, and can be associated with other movement disorders.[3] In our patient, the age of onset, the irresistible urge to move and the ability to suppress it, the stereotypic and nonrhythmic presentation, and the absence of the drawing and pulling sensation of dystonia make the diagnosis of motor tic very clear.

We also think that the buccal movement was a new tic and not a neuroleptic-induced dystonia. Dystonia usually occurs within 48 hours in 50% of patients treated with neuroleptics, and in 90% of these patients, an acute dystonic reaction develops within five days.[4(p604)] Our patient developed a mouth twitching after seven days of treatment with haloperidol. This stereotypic buccal movement was involuntary, rapid, recurrent, nonrhythmic, and could be voluntarily suppressed. An irresistable urge to move would develop, however, that would only be relieved by twitching his mouth. Therefore, our patient had a "new tic," not an acute neuroleptic-induced dystonia.

As stated by Wasserstein and Honig, chronic motor tic should be differentiated from dystonia. Treating each disorder can be different, and both conditions can be exacerbated by stress and haloperidol.[5] Prophylaxis with anticholinergics can prevent neuroleptic-induced dystonias, but it is not known if anticholinergic prophylaxis could prevent an exacerbation of motor tics or the development of new tics. Acute neuroleptic-induced dystonic reactions can be treated with intramuscular anticholinergics, diphenhydramine, diazepam, or amobarbital,[2] whereas an exacerbation of motor tics and the development of new tics usually indicate discontinuing the drug.

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Nintendo Elbow

To THE EDITOR: Complications of Nintendo range from the socially unacceptable (enuresis)[1] to the more socially unacceptable (encopresis)[2] to the distressing (seizures),[3] along with various musculoskeletal syndromes.[4-6]

We report a more benign variant, Nintendo elbow.

The patient, a 12-year-old boy, reported right elbow pain for several days. His father stated that the discomfort had been present for at least a month. The boy's only physical activity during this period was playing Nintendo "a lot." The

child was otherwise healthy, taking no medications, and had no allergies.

Examination revealed tenderness with slight swelling proximal to the olecranon. The patient reported increased pain with flexion and extension against resistance.

Treatment consisted of the administration of ibuprofen and discontinuation of the precipitating trauma. On follow-up nine days later, the syndrome had resolved. Long-term recommendations included support of the elbow on a firm surface during Nintendo playing and the use of nonsteroidal medication as needed.

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Primary Care Professionals' Attitudes Regarding Compulsory HIV Testing

To THE EDITOR: In 1991, as part of a larger human immunodeficiency virus (HIV) needs assessment survey of Washington State health care professionals' knowledge, attitudes, and training, 3,060 currently licensed Washington State primary care professionals identified as either dentists, dental hygienists, physicians, physician assistants, nurses, or nurse practitioners were surveyed by mail regarding their attitudes about compulsory testing of all hospital admissions, surgical admissions, all health care workers, and health care workers who do invasive procedures.* Of the primary care professionals surveyed, 36% completed and returned the anonymous survey within the time allowed. Response rates varied among professional groups, with dental hygienists and nurse practitioners providing the highest response rates (55% and 46%, respectively) and physicians providing the lowest (31%).

Most of those who responded worked in an urban community (77%) and in either a hospital (32%) or in private practice (33%); 37% completed their professional training after 1979 and 26% before 1970. Nearly all (96%) had attended conferences or presentations on the acquired immunodeficiency syndrome (AIDS), and 37% reported having been tested for HIV. Of those who responded, 31% and 44% reported not ever having knowingly worked with any HIV-seropositive or AIDS patients, respectively.

Support for compulsory testing was lowest for the indiscriminate testing of all health care professionals (39%) and highest for the testing of persons admitted to hospital for surgical procedures (51%). Of the combined sample, 45% supported compulsory testing of all hospital admissions; 43% supported the testing of health care professionals who do invasive procedures.

χ_2 Analyses indicated significant differences among groups in attitudes regarding compulsory testing of all hospital admissions ($P = .001$), all surgical admissions ($P = .001$), and all health care professionals ($P = .006$). Dentists, more than any other professional group, supported compulsory testing. No significant differences among groups were found in attitudes regarding compulsory testing of health care professionals who do invasive procedures.

Significantly discrepant views were found in the combined sample's attitudes regarding compulsory testing of all health care professionals versus those who do invasive procedures, all hospital admissions versus surgical admissions, and all hospital admissions versus all health care professionals. There was significantly more support for testing health care professionals who do invasive procedures than all health care professionals ($P = .001$), testing those admitted for surgical procedures than all hospital admissions ($P = .001$), and testing those admitted to hospital than all health care professionals ($P = .001$).

Health care professionals in private practice favored the compulsory testing of all populations significantly more than did those working in hospitals, clinics, and other practice settings ($P \leq .01$). Similarly, those who had not worked with any HIV-positive or AIDS patients favored testing all populations significantly more than those who had worked with HIV-positive or AIDS patients ($P \leq .01$). Those who reported having been tested for HIV favored compulsory testing of all persons admitted to hospital and all health care professionals significantly more than did those who had not been tested ($P = .001$). In general, rural professionals and those who completed their professional training before 1979 tended more than their counterparts to favor testing.

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More on the Gag Rule

To THE EDITOR: This is in response to Dr Hammons's letter[1] in the December 1991 issue regarding the Supreme Court upholding the government's regulations that physicians at family planning clinics should no longer receive federal funds if they discuss abortion with their patients. Dr Hammons writes, "If I and many Americans like me choose to believe that abortion is not a viable alternative for unexpected pregnancies, then one of the ways that we support our beliefs is by insisting that we should not have to pay for such counseling through our tax dollars."

If I and many Americans like me, as Jehovah's Witnesses, choose to believe that blood transfusions are not a viable option during a surgical procedure, should clinics that receive federal funds no longer be permitted to *discuss* blood transfusions? And those many American Latter Day Saints who choose to believe that artificial birth control is not a viable option? If small (or large) groups of religious American zealots are allowed to dictate what medical or surgical options may be discussed by physicians who work in federally funded clinics, we will be unable to provide the best medical care available for those patients.

I agree with Dr Hammons that this is not a freedom of speech issue. It is an attempt by a religious minority to force its beliefs on others.

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REFERENCE

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Lessons From the Practice

The Craft

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He had been a large, imposing man. The cancer had consumed the sturdy, muscular substance of his bulk. Left behind was sallow, unnaturally aged flesh drooping over the rafters and beams of his face and skeleton. His hands were large, with thick tapered fingers that retained, ironically it seemed, their appearance of strength. But they looked unnatural, hinged to spindly forearms that were at one time powerful and brawny.

He was admitted with metastatic lung cancer and a new pneumonia. Since his diagnosis six months before, he had been in and out of the hospital for x-ray therapy, pleural effusions, and finally, a superimposed pneumonia. The weary house staff, having briefly presented the patient's case to me, were occupied elsewhere with the work of discharging patients and writing orders for the day.

He stared keenly out the window. Despite his wasted condition, I had a sense, based on nothing but my experience with people and the suffering of patients, that Mr Casey wanted not so much to be "cured," but to be productive once again and to leave the idleness of the hospital routine.

I was discouraged by the fact that we could treat the pneumonia but in no way alter the work of his cancer. How gratifying it must be to repair arteries, pin bones, replace heart valves. The act of using your hands to restore health, to physically rearrange disordered body parts, seemed comforting and simple. Not so with internal medicine. His cancer had overwhelmed Mr Casey, and, medically, I had little to offer. How could I help him?

"Mr Casey, what kind of work do you do?" I asked, trying to draw him out.

Immediately he brightened and turned his attention away from the busy streets outside. "I'm a carpenter, Doc. I can build anything with wood. I started with my dad's rule and saw, and now I make cabinets to order. You should see my work."

Impressed by this burst of enthusiasm, I was anxious to hear more. "Tell me what it's like," I said, leaning forward earnestly.

For the next 30 minutes, I entered my patient's world of craftsmanship. He described the years of journeyman carpentry, the thrill of putting up a house, and his pride in creating cabinets of his own design. He took a picture album from his bedside stand and showed me photos of his work, some completed, other pieces half finished. There was pride and dignity in his face despite the shrunken, distorted features.

I was deeply moved by this candid, totally honest display of himself and what he believed in. The real tragedy was the loss of this skill, of his craft, to cancer. He didn't fear death but was tortured by his forced inactivity; he had been robbed of purpose.

"What do you want to do when you get out of the hospital?" I wondered aloud. Could I somehow focus him on something?

He made an attempt to smile. "Well, I think I'll finish that dining room hutch I showed you. Then I'll take a picture of it and let you see it."

"I'll look forward to it," I answered. "We can't cure your cancer, but we will help you get home and back to your shop." I stood up to leave.

"Thanks a lot, Doc."

We shook hands. His substantial, calloused grip enclosed my soft, fleshy hand. For a moment I envied him his talents and his art. I glanced back at Mr Casey from the door and watched him study his photos. I realized I had been practicing my craft and didn't even know it.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

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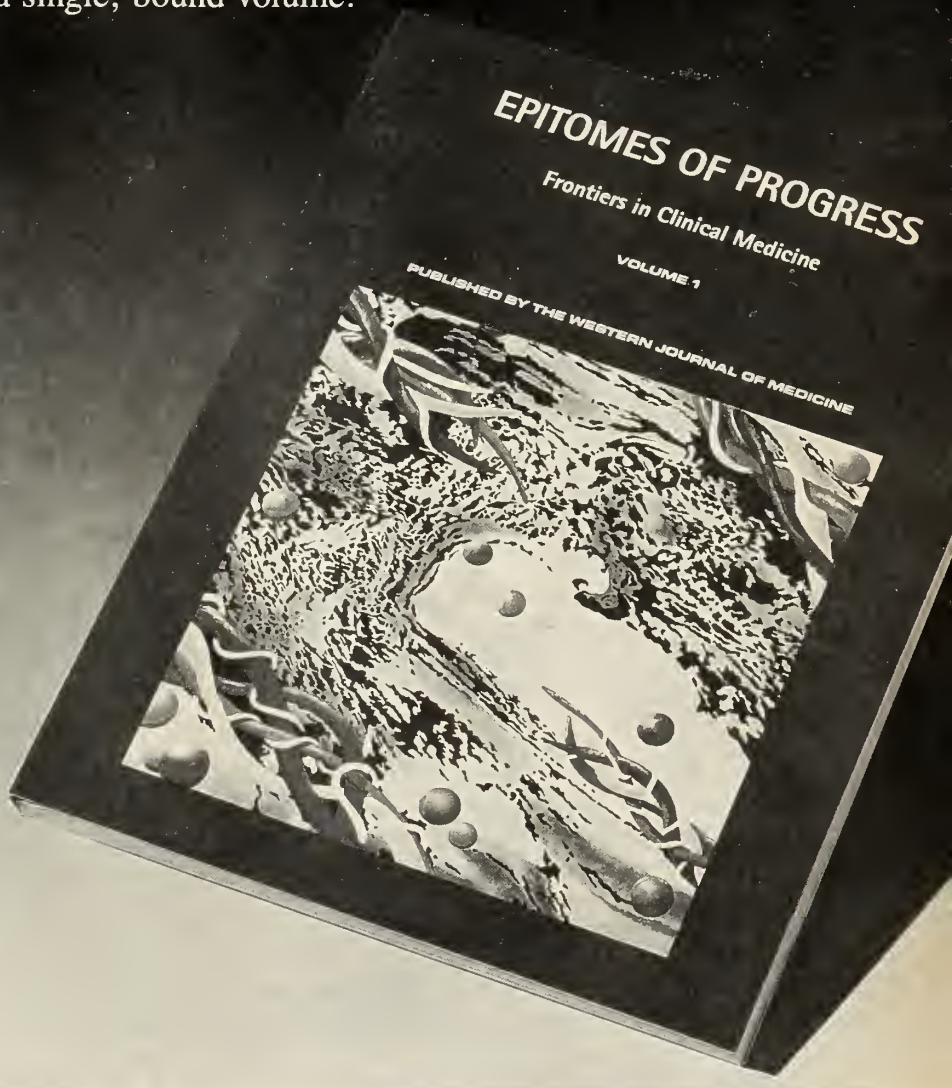

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3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

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7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year).

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

CHECKLIST

- Original manuscript and 2 copies
- **Everything** double-spaced
- Illustrations, black and white glossy, identified with lead author's name—3 sets, plus figure legends that describe fully and in complete sentences what the figure depicts
- Letter of transmittal that includes release of copyright, statement of conflict of interest, and authorship responsibility, **signed by all authors**
- A 200-word abstract
- Title page that includes current affiliation of all authors and address **and telephone number** for corresponding author
- Permission-to-borrow letters for any previously published illustrations or tables
- All references numbered consecutively, double-spaced, and cited in text. No unpublished data or nonscientific publications listed in references (include in text)

CONTINUING MEDICAL EDUCATION

(Continued from Page 600)

September 21-26 & October 19-24—**Lactation Management Education Program.** UCSD at Wellstart, San Diego. Mon-Sat. Contact: UCSD.

October 19-22—**17th Annual Pediatrics for the Practitioner.** Long Beach Memorial at Mauna Kea Beach Hotel, Kamuela, Hawaii. Contact: Eunice Larson, MD, (310) 595-3422.

PSYCHIATRY

July 24-28—**13th International Congress on Child and Adolescent Psychiatry: Violence and Vulnerability.** UCSF at Fairmont Hotel, Nob Hill, San Francisco. Fri-Tues. Contact: UCSF.

August 4-9—**Neuropsychiatric Aspects of Politics and Politicians.** American Academy of Family Physicians and Southern California Neuropsychiatric Institute at Mauna Kea Beach Hotel, Kamuela. Tues-Sun. 22.5 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

August 7-11—**The Power of the Art—Suggestive Therapeutics: An Introduction to Medical Hypnosis.** UCSD at Mission Bay Hilton, San Diego. Fri-Tues. Contact: UCSD.

November 13-15—**38th Annual Group Therapy Symposium.** UCSF at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. Contact: UCSF.

PULMONARY MEDICINE

September 17-19—**11th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $410. Contact: UCSF.

RADIOLOGY

July 17-19—**Vascular Imaging and Intervention for the '90s.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Fri-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-22—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Mon-Wed. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-24—**Clinical Imaging for the Non-Radiologist.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Quail Lodge, Carmel. Thurs-Sun. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 27-August 1—**Advanced Neuro MRI—Beyond Spin Echo and Musculoskeletal MRI.** Hoag Memorial Hospital Presbyterian at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Sat. 32 hrs. $645. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 10-14—**Radiology & Clinical Correlation for Non-Radiologists.** UCSD at Hotel Del Coronado, San Diego. Mon-Fri. Contact: UCSD.

September 9-11—**8th Annual Sonography Update.** UCSD at Hotel del Coronado, San Diego. Wed-Fri. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 12-13—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 21-23—**Digital Radiography and Image Management Networking.** UCLA Radiological Sciences at Miramar Sheraton Hotel, Santa Monica. Mon-Wed. 16 hrs. $345. Contact: UCLA Radiological Sciences, (310) 206-7435.

October 1-4—**Western Neuroradiological Society Annual Meeting.** Western Neuroradiological Society at Ritz-Carlton, San Francisco. Thurs-Sun. 11.5 hrs. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 24-25—**Musculoskeletal Imaging.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-30—**17th Annual Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 25.25 hrs. $600. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 30-November 1—**12th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 2-6—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Mon-Fri. 15 hrs. $400. Contact: UCSD.

SURGERY

June 25-27—**9th Annual Meeting on Arthroscopic Surgery of the Shoulder.** UCSD and Tri-City Orthopaedic Surgery Medical Group at Hyatt Regency, La Jolla. Thurs-Sat. Contact: James Esch, MD, 3905 Waring Rd, Oceanside 92056. (619) 940-2066.

September 14-18—**What's New in Vascular Surgery: A Comprehensive Review and Update.** UCLA at Miramar Sheraton, Santa Monica. Mon-Fri. 34 hrs. $469-$625. Contact: UCLA Extension.

October 31-November 7—**14th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott, Maui, Hawaii. 1 week. Contact: UCLA Extension.

GENERAL/MULTIDISCIPLINARY

July 12-17—**21st Annual Summer School of Alcohol, Tobacco and Other Drugs.** UCSD. Sun-Fri. Contact: UCSD Extension.

October 22-25—**American Pain Society: 11th Annual Meeting.** American Pain Society at San Diego. Thurs-Sun. Contact: APS, 5700 Old Orchard Rd, Skokie, IL 60077-1057. (708) 966-5595.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 19-20—**Neonatal Resuscitation Course.** Children's Hospital of Denver in Laramie, Wyoming. Fri-Sat. Contact: Lois Pine, (303) 777-7166.

June 23-25—**Community Health Traineeship.** Children's Hospital, Denver. Tues-Thurs. Contact: Pat Winter, (303) 861-6668.

July 9—**Cultural Considerations in Perinatal Nursing.** Children's Hospital at University Hospital, Denver. Thurs. Contact: Trish Beachy, (303) 270-8376.

August 17-21—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

September 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

September 16-17—**Neonatal Resuscitation Hospital-Based Instructor Course.** Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

September 17, 24, October 1, 8—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Four consecutive Thursdays. Contact: Trish Beachy, (303) 270-8376.

October 23-24—**Fifteenth Annual Perinatal Conference.** Children's Hospital of Denver in Fort Collins. Fri-Sat. Contact: Sharon Adams, (303) 861-6946 or (800) 225-0010.

November 19-22—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

November 30-December 4—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

(Continued on Page 685)

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CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. **Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reportec placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg v rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM Capsules involving over 3000 patients, the most common events (ie, grea than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthe (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5 nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%)

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degre bundle branch block, congestive heart failure, ECG abnormalit hypotension, palpitations, syncope, tachycardia, ventricu extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnorma hallucinations, insomnia, nervousness, paresthesia, personality chan somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, n elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hep warnings), thirst, vomiting, weight increase

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritatio hyperglycemia, hyperuricemia, impotence, muscle cramps, na congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliat dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anem increased bleeding time, leukopenia, purpura, retinopathy, a thrombocytopenia. In addition, events such as myocardial infarction h been observed which are not readily distinguishable from the natural hist of the disease in these patients. A number of well-documented cases generalized rash, characterized as leukocytoclastic vasculitis, have be reported. However, a definitive cause and effect relationship between th events and CARDIZEM therapy is yet to be established

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 r 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsu of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 100.

CARDIZEM® CD Product Information as of October 1991

CARDIZEM® SR Product Information as of January 1991

References: 1. Data on file, Marion Merrell Dow Inc 2. Cramer JA, Mattson Prevey ML, et al JAMA 1989;261(22):3273-3274

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY MO 64114

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CONTINUING MEDICAL EDUCATION

(Continued from Page 682)

IDAHO

July 30-August 1—**Idaho Medical Association—Annual Meeting.** Coeur d'Alene. Thurs-Sat. Contact: Idaho Medical Assn, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 13-17—**Imaging 1992: Ultrasound, CT, MR, and Mammography.** Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 7-11—**Mammography Update.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 688)

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"QA/UR ISSUES IN MANAGED CARE"

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(Continued from Page 685)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

June 21-27—**School on Alcoholism, Drug Dependencies** (Sponsor: UUSM). Sun-Sat. U of U Browning Auditorium. Contact: UUSM.

June 24-27—**Slice of Life: Interactive Video and Related Multimedia Technology in Health Education** (Sponsor: UUSM). Wed-Sat. U of U Eccles Genetics Auditorium. Contact: UUSM.

July 12-17—**Update in Internal Medicine Focus on Ambulatory Care Medicine** (Sponsor: UUSM). Sun-Fri. Snowbird. Contact: UUSM.

July 31-August 1—**UOS Shakespearean Festival Meeting** (Sponsor: UOS). Fri-Sat. Contact UOS.

August 6-8—**ISLD Dental Congress** (Sponsor: UUSM). Tues-Sat. Marriott Hotel, Salt Lake City. Contact: UUSM.

September 10—**Monthly Meeting** (Sponsor: UOS). Thursday evening. Contact: UOS.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.
WRI:	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 18-20—**Diabetes Update.** Seattle. Thurs-Sat. Contact: U/W.

June 22-23—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: PCMS.

June 25-27—**Refocus on Women's Health Care.** Seattle. Thurs-Sat. Contact: U/W.

June 26—**Sports Medicine.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

July 23-26—**Current & Emerging Issues in Cancer Pain.** Seattle. Thurs-Sun. Contact: U/W.

July 29-31—**STD Update.** Seattle. Wed-Fri. Contact: U/W.

July 30-August 1—**STD Update.** Seattle. Wed-Fri. Contact: U/W.

August 3-8—**Summer Seminar in Medical Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 21-22—**Regional CME Network Meeting.** Seaside, Oregon. Fri-Sat.

September 14-18—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

September 23-24—**Critical Care.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

October 1-4—**Washington State Medical Association Annual Meeting.** Yakima. Thurs-Sun. Contact: WSMA.

October 15-17—**Endoscopic Sinus Surgery.** Seattle. Thurs-Sat. Contact: U/W.

October 22—**General Surgery Review.** Everett. Thurs. Contact: PNMEI, (206) 258-6322.

October 23—**Perinatology.** Fri. Tacoma. Contact: Multicare, (206) 594-1221.

November 12—**Dermatology.** Thurs. Everett. Contact: PNMEI, (206) 258-6322.

November 12-13—**Advances in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 20—**Orthopaedic Trauma Update.** Spokane. Fri. Contact: U/W.

December 4-5—**Urology Annual Meeting.** Vancouver, BC. Fri-Sat. Contact: NWUS, (206) 441-9762.

December 10-12—**8th Infectious Disease Conference.** Thurs-Sat. Everett. Contact: PNMEI, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

August 24-26—**Eighteenth Annual Tutorials in the Tetons.** Jackson Lake Lodge, Moran. 14.5 hrs. Contact: American College of Cardiology, (800) 257-4739. ◆

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PEDIATRICIAN—SANTA MONICA. Associate needed for rapid takeover of busy, lucrative Pediatric practice. Good coverage weekends. Low overhead. Rare opportunity. Phone Lisa; (310) 829-1752 for details.

BC/BE RADIOLOGIST. Exceptional northern California location. General diagnostic radiology, including invasive. All imaging modalities represented. Academic appointment available. Join three BC Radiologists. Contact Carol Westfall, Cejka & Co, 222 S Central Ave, Ste 700, St Louis, MO 63105; phone (800) 765-3055, FAX (314) 726-3009.

IMMEDIATE OPPORTUNITY for BC/BE Primary Care physician in expanding "group without walls" in Glendale, California, twenty minutes north of downtown Los Angeles. Salary plus incentive plus benefits. No buy-in necessary. Contact Director, Physician Services, Glendale Memorial Hospital, (818) 502-2371.

100 MEMBER multispecialty group seeks BC/BE Family Practitioners, Pediatricians, General Internists, Otolaryngologist, and Dermatologist in pleasant, growing northern California community two hours from San Francisco, Yosemite, and the Sierras. Excellent benefits, salary and facilities. Send CV to C. V. Allen, MD, Medical Director, 600 Coffee Rd, Modesto, CA 95355.

SOUTHERN CALIFORNIA. Family Practitioner BC/BE or General Practitioner. Multispecialty group in Orange County. Excellent compensation. Call (714) 633-4225.

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SAN JOSE. Leading Primary Care group practice affiliated with 200-bed hospital is growing. BE/BC physicians in the following specialties are needed:

- Family Practice
- Internal Medicine
- Pediatrics
- OB/GYN

A generous salary, outstanding benefits, and a liveable practice schedule are offered. Please send your CV to **Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111;** or call **(800) 229-0411** or **(415) 399-8840; FAX (415) 399-0411.**

NEPHROLOGIST WANTS PARTNER/ASSOCIATE BC/BE Gastroenterologist/Cardiologist/Nephrologist/Pulmonologist. Excellent practice, equal partnership opportunity without buy-in or overhead. Send CV to Dr M. Streger, 27800 Medical Center Rd, Ste 122, Mission Viejo, CA 92691.

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full-/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

BEAUTIFUL OREGON COAST. Private multispecialty cooperative with excellent facility seeking Family Practice physician to join five full-time Family Practitioners. Full spectrum of Family Practice. In-house lab, x-ray, day surgery. Contact Marce Knight, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294 or (800) 234-1231.

POSITIONS AVAILABLE FOR EMERGENCY PHYSICIANS WORKING PM SHIFTS. Hourly differential paid in addition to fee-for-service compensation. Shifts vary from seven to nine hours in length. Excellent fringe benefits. Malpractice paid. Contact Nancy C. Kendall at SPEMG, Inc, 8350 Auburn Blvd, Ste 100, Citrus Heights, CA 95610; or call (916) 727-1049 for more information.

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- ORTHOPEDIC SURGERY
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- ONCOLOGY (some general Internal Medicine necessary initially)

These excellent practice opportunities offer guaranteed income and a strong referral base.

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 105,000; a growing area with new businesses and a stable economy. A 30% plus growth in population and jobs is predicted for our area during 1990s.

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Contact:

Tulare District Hospital
Physician Recruiting Office
PO Box 90112
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(800) 468-2687

DERMATOLOGIST. Immediate opportunity available for full- or part-time position with University affiliated multispecialty group in one of the most desirable cities. We offer a balanced lifestyle, competitive salary and an excellent benefit package. Send CV to Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

BE/BC FAMILY PRACTITIONER to join one Family Nurse Practitioner, one Pediatric Nurse Practitioner and one OB/GYN Nurse Practitioner, and two part-time OB/GYNs in Walla Walla, Washington. Share call with four practitioners. Competitive salary, excellent benefit package, including vacation up to 32 days per year and professional liability. Public Health Service immediate Loan Repayment slot. Contact Sylvia Arroyo, Clinic Administrator, Family Medical Center, PO Box 515, Walla Walla, WA 99362; (509) 525-6650, or Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant; (509) 865-5898.

BC/BE OB/GYN with commitment to caring for the underserved, needed to join 13 physician (OB, Family Practitioner, Pediatrics, Internal Medicine) Primary Care community health clinic in Toppenish, Washington. Rural setting, beautiful, sunny, central Washington near Columbia River gorge. Diverse cultural influences (Hispanic and Native American). Recreational opportunities including fishing, skiing, and bikers' paradise. Competitive salary with excellent benefit package including vacation up to 32 days per year and paid professional liability. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

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DEAR DOCTOR:

If your goals include a quality lifestyle, a dynamic medical community, excellent schools/universities, and beautiful and affordable housing, then we have the ideal practice opportunity for you!

HOLY FAMILY HOSPITAL and the MEDICAL STAFF are working together to meet the healthcare demands of our 150,000 patient population. There is an IMMEDIATE need for BC/BE physicians in the following specialties:

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- INTERNAL MEDICINE
- CARDIOLOGY
- PSYCHIATRY
- GENERAL SURGERY
- PLASTIC SURGERY

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CONTACT with CV to: **Nancy Chaffins**

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BC/BE FAMILY PHYSICIAN needed for large multispecialty group in San Jose, California. Includes Internal Medicine, Pediatrics, Gynecology, minor surgery with inpatient/outpatient responsibilities. Opportunities exist at main location and smaller facilities. Good call coverage exists. Competitive salary and benefits offered. Call Florence Korbus collect at (408) 999-7113 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

SAN JOSE (SANTA CLARA COUNTY). Exceptional opportunity for a BC/BE Occupational Medicine Physician to become the medical director of an established Occupational Medicine program in a group practice. See patients and participate in management and growth of the program in an excellent market. Send CV to Number 267, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NORTHERN CALIFORNIA. Successful solo seeks successor. Outstanding Family Practice in San Francisco suburban neighborhood. Excellent patient mix without HMO contracting. Shared call every 5th. Hospital will assist with the start-up. Contact and send CV to Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

PEDIATRICIANS—NEVADA, CALIFORNIA, LOUISIANA, TEXAS! Private practice opportunities available. Hospital sponsored with coverage or join an established group. For details, call Eloise Gusman; (800) 535-7698 or send CV to PO Box 101656, Ft Worth, TX 76185.

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Submit resumé, including background and cover letter, in confidence to:

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Sandra Chester, Administrator
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CENTRAL CALIFORNIA OCCUPATIONAL/FAMILY PRACTICE OPPORTUNITY. Growth oriented, dynamic group seeking BE/BC physician for Urgent Care/Occupational/Family Practice setting. Bilingual Spanish a real plus. Excellent salary, benefits, vacation, educational leave, paid malpractice. Please call (805) 322-2273, or send CV to Linda Brobst, Southwest Urgent Care, 5397 Truxtun Ave, Bakersfield, CA 93309.

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INTERNIST OR FAMILY PHYSICIAN. Position available immediately. Nationally recognized comprehensive health care program for frail elderly residing in the northeast sector of San Francisco seeks Internist or Family Practice Physician for full-time employment. Work with a collegial, multidisciplinary team. Send CV to Darlene Yee, On Lok, Inc, 1441 Powell St, San Francisco, CA 94133. EOE.

GERIATRICS FACULTY POSITION. The University of California, Davis, School of Medicine is recruiting for a full-time faculty position at the Assistant/Associate/Professor level to assist in an expanding Geriatric program at UCD. The School has a major commitment to Geriatric Medicine and has already established a Center for Aging and Health. The candidate must be BC/BE in Internal Medicine with appropriate experience in an academic Geriatric/Gerontology Program and must qualify for California licensure. A letter outlining research, teaching interests, geriatric experience and a CV must be received by July 31, 1992. Send reply to Calvin H. Hirsch, MD, Internal Medicine, 2221 Stockton Blvd, Rm 3107, Sacramento, CA 95817. The University of California is an Affirmative Action Equal/Opportunity Employer.

NORTHERN CALIFORNIA

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FAMILY PRACTICE RESIDENCY FACULTY POSITION. FULL-TIME ASSOCIATE PROFESSOR. UNIVERSITY OF WYOMING FAMILY PRACTICE RESIDENCY PROGRAM-CASPER. This is an outstanding rural Family Practice Residency Program with 24 residents and nine faculty members. It is affiliated with Wyoming Medical Center, which is currently undergoing a $20,000,000 expansion. Responsibilities include resident supervision in ambulatory and inpatient settings, participation in clinical research projects, direct patient care, and administrative duties. Requirements include BC, a minimum of three years of Family Practice including Obstetrics, and a strong desire to teach rural family medicine. Applicants should include current CV and three references. Competitive salary and benefits. Come join us in beautiful Wyoming. The University of Wyoming is an equal opportunity/affirmative action employer. Final approval will be made by the University of Wyoming. Please contact Jay Swedberg, MD, Acting Program Director, University of Wyoming Residency Program-Casper, 1522 E. A St, Casper, WY 82601; (307) 266-3076.

ESCAPE those urban hassles and come to scenic northern California and Phoenix, Arizona. Opportunity available to join two other Internists in private practice. Competitive salary and benefit package available. Contact Mark Oswald of Gielow/Laske Associates, Inc, 306 N Milwaukee St, Milwaukee, WI 53202; (800) 969-7715, FAX (414) 226-4131. Confidential inquiries welcome.

CALIFORNIA. The Sacramento Children's Medical Clinic, an ambulatory private practice for children of low income parents, consisting of four offices (one on wheels) needs a BE/BC General Pediatrician. Direct patient care and supervising midlevels for inner city, migrant health and outreach programs. Monday through Friday. Quake-free locale. Spectacular climate. Innumerable recreational opportunities. Competitive salary with equity potential. Contact Gilbert Simon, MD, 1355 Florin Rd, Ste 14, Sacramento, CA 95822, (916) 422-6326.

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PHYSICIAN
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Physicians wanted for rewarding work. Duties include: Case review to determine medical necessity/appropriateness of service by health care providers for Medi-Cal covered services; providing input into development of policies in the administration of medical aspects affecting the Department's programs; interfacing with provider groups, hospitals, QA/UR committees, and medical societies to encourage the delivery of quality care to Medi-Cal patients. Monthly salary: $6,149 to $8,034, plus attractive retirement/fringe benefits.

Positions exist statewide. Applications (std 678) may be obtained from any Employment Development Department Office. Send application/CV to: Department Health Services, Field Services Branch, 714 P St, #1516, Sacramento, CA 95814. Applications must be received by June 23, 1992.

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SEATTLE. As the result of population growth and reputation, this 28 physician group practice is in need of several recently trained Family Practitioners. This suburban community is situated within minutes of downtown Seattle and within one hour of Mt. Rainier. Remuneration package includes base salary plus incentive and full benefits with partnership after two years. Call rotation every 7th night and weekend. Congenial atmosphere. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

FAMILY PRACTICE—NORTHERN CALIFORNIA BC/BE. Immediate opportunity for an associate. All negotiable proposals considered. Advance to partnership in very lucrative and exciting practice located 30 miles east of San Francisco next to 300-bed hospital. Send CV to Fred Von Stieff, MD, Mount Diablo Hospital, 2540 East St, Concord, CA 94520; (510) 680-8933.

THE MEDICAL CENTER AT PRESCOTT, ARIZONA is recruiting for a Physician, BC/BE, in Internal Medicine, Family Practice, or Geriatrics. The Medical Center is comprised of a 217-bed General Medical and Surgical Facility with a 60-bed Nursing Home Care Unit and a 208-bed Domiciliary. Salary negotiable. Send CV to Rita Heidisch, MD, Acting Chief of Staff, VA Medical Center, Prescott, AZ 86313, or call (602) 776-6009. An equal opportunity employer.

INTERNAL MEDICINE—Southern California. Challenging career opportunities for specialists in Internal Medicine desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

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YOSEMITE. Yosemite Medical Clinic is seeking a fourth full-time staff physician experienced in Primary and Emergent Care. ACLS required, ATLS or PALS helpful for occasional emergencies. All outpatient based. Housing provided in Yosemite Valley. Contact Robin Berman; (209) 372-4637, PO Box 547, Yosemite, CA 95389.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

CALIFORNIA MULTISPECIALTY. Dermatologist, Radiologist, Otorhinolaryngologist, General Surgeon, Cardiologist, Internal Medicine, Pediatrician, Gastroenterologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

OB/GYN—Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE Physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

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BE/BC UROLOGIST to join busy 28 doctor multispecialty group practice. Excellent practice opportunity, full range of benefits, early partnership status. For more information contact Shane Spray, 1400 Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

(Continued on Page 692)

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GREAT OPPORTUNITIES IN NORTHERN CALIFORNIA

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We offer competitive salary, a comprehensive benefits package including retirement and 401K plan contributions, and early access to partnership and stockholder status.

The South Bay area provides a wide range of cultural and recreational activities, good schools, fine dining, and a congenial climate.

If you are committed to excellence and strongly motivated for success, we'd like to hear from you. Send your CV to Maureen Forrester, San Jose Medical Group,* 45 S. 17th St, San Jose, CA 95112; or **call (408) 282-7833.**

*An independent physician group affiliated with Stanford University Medical Center

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ROCKWOOD CLINIC, P.S., a well-established multi-specialty group seeks BC/BE family physicians for busy, well-equipped satellite clinics located in a rapidly growing area with strong economic growth and favorable CALL schedule. Excellent benefit package includes salary commensurate with experience leading to early shareholder status.

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CONTACT: Colleen Mooney, Recruitment Coordinator.

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Internist wanted for beautiful Salt Lake City area. Excellent skiing, camping, fishing and hunting. Looking for aggressive, hard-working Family Practitioner to expand clinic. Complete laboratory facilities and x-ray in ambulatory care type setting. Call or write: **Robert Davis, MD, Director, Family Medical Center, 1519 W. 9000 South, West Jordan, UT 84088; (801) 562-9100.**

BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

BC/BE GENERAL INTERNIST NEEDED. Nine physician department in 27 doctor multispecialty clinic. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

AMBULATORY CARE, Hayward, Modesto, Orange County, California. Thriving practices, attractive facilities, competitive salary, profit-sharing, partnership with growth potential. Contact Robin Morgan, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612; (510) 835-7431. Outside of California, (800) 842-2619.

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OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

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BC/BE FEMALE INTERNIST sought to join established female Internist in a southern California private practice. Send CV to Number 261, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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GENERAL INTERNIST in the Pacific Northwest. Busy 30 physician multispecialty group practice looking for General Internist with ICU skills and interests to join existing Internal Medicine department. Competitive salary and benefits. Send CV to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

BC/BE FAMILY PHYSICIAN to join three other Family Practitioners, OB/GYN, Internist, and Physician Assistant at busy Migrant/Community Clinic in Grandview, Washington. Full-range Family Practice, including Obstetrics, hospital work, and Emergency coverage. Excellent relationship with well trained BC Family Practitioners and surgeon in community. Friendly rural area with good schools. Close to mountain recreational areas and water sports. Professional liability paid. Excellent benefits, vacation liberal. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

NEED ASSOCIATE to join busy dermatology practice in Santa Barbara, California. Will also consider sale at a reasonable price. Excellent opportunity to live in a beautiful seaside community. Call Dr Senn at (805) 569-0186 or evenings at (805) 565-3908.

EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ACADEMIC PULMONOLOGIST/INTENSIVIST. Academic Pulmonary/Critical Care physician needed to join a three physician division of Respiratory and Critical Care Medicine at a 400-bed teaching hospital with Stanford University affiliation. The hospital has a full Internal Medicine residency training program and the division is part of a combined three hospital Pulmonary fellowship (SCVMC, Stanford University, and Palo Alto VA). The division's activities include supervision of medical students, residents and fellows, direction of a complete PFT LAB and an eight-bed MICU and participation in clinical research. Address inquiries to Carl M. Kirsch, MD, Division of Respiratory and Critical Care Medicine, Santa Clara Valley Medical Center, 751 S. Bascom Ave, San Jose, CA 95128; or call (408) 299-5514. An equal opportunity and affirmative action employer.

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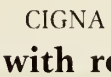

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or Julie Wagner, Provider Relations Coordinator
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(714) 883-8711, ext 3063

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PHYSICIANS WANTED

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We are seeking motivated Primary Care physicians to join our growing Urgent/Primary Care clinic. BC/BE physicians in the field of Internal Medicine, Family Practice, or Occupational Medicine are invited to apply.

The Cupertino Medical Center is located in the heart of Silicon Valley and is a leader in the provision of Urgent Care and Primary Care services. You will lead a team of health care professionals, work in a pleasant, modern environment, and enjoy the opportunity provided by our established base of loyal patients.

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Direct inquiries to Mark Congress, MD, Medical Director
20289 Stevens Creek Blvd, Cupertino, CA 95014, (408) 996-8656

EMERGENCY MEDICINE UNIVERSITY POSITION. The University of California, Davis, School of Medicine, is recruiting for a full-time faculty. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine and Clinical Toxicology is undergoing rapid academic development and has an approved residency program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in Northern California. The Department is a Paramedic Base Station and Training Center, and in addition, has an active Helicopter Service and Regional Poison Center. Candidates must be BC/BE in Emergency Medicine and be eligible for licensure in California. A letter outlining teaching background, interests, experience, and research in addition to a CV and the names of five references should be sent to Robert W. Derlet, MD, Chair, Emergency Medicine Search Committee, Tr 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817. Applications will not be accepted after August 1, 1992. The University of California is an Affirmative Action/Equal Opportunity Employer.

PRIMARY CARE PHYSICIAN, OSTEOPATHS, AND PHYSICIAN ASSISTANTS wanted for expanding eastern Washington clinic. Full- and part-time positions available. Located in prime recreational area. Skiing, sailing, fishing, hunting all within a short distance. Enjoy mild climate, excellent schools and a major university branch campus in growing community of 100,000 plus. Challenging work in a superbly equipped clinic with state-of-the-art lab, x-ray, laser, and endoscopy. Above average compensation and benefits including malpractice, health insurance, and CME. Contact Dr Stephen L. Smith, 310 Torbett, Richland, WA 99352; (509) 545-8340 or FAX (509) 946-7666.

BC/BE OB/GYN to join one Internist, one Family Nurse Practitioner, one Pediatric Nurse Practitioner, and one OB/GYN Nurse Practitioner in Walla Walla, Washington. Shared call with two local OB/GYNs. Competitive salary, excellent benefit package, including vacation up to 32 days per year and professional liability. Public Health Service immediate loan repayment slot. Contact Sylvia Arroyo, Clinic Administrator, Family Medical Center, PO Box 515, Walla Walla, WA 99362; (509) 525-6650, or Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant; (509) 865-5898.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

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BC/BE FAMILY PRACTITIONER for satellite clinic of prestigious multispecialty group practice. Join one other Family Practitioner and one Physician's Assistant in small town setting with urban culture 20 minutes away. Generous benefit package. Send CV to Donald Benz, MD or Karen Stanton, The Vancouver Clinic Inc, PS, 700 NE 87th Ave, Vancouver, WA 98664; (206) 254-1240.

FULL-TIME, non-tenured track position to work as an attending physician in the Division of Emergency Medicine, Department of Surgery at the University of Utah School of Medicine/teaching hospital. Must be residency trained or BC in Emergency Medicine. Reply to MS Linscott, Jr, MD, 50 N Medical Dr, Salt Lake City, UT 84132; (801) 581-2730. Position will be open June 15, or until suitable candidate is identified. The University of Utah is an Affirmative Action/Equal Opportunity Employer.

SOUTHERN CALIFORNIA. Family Practice physician position available in Riverside County. Guaranteed income, excellent benefits with early partnership. Send résumé to Number 265, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FULL-TIME BC/BE DIAGNOSTIC RADIOLOGIST needed to replace retiring senior partner in a friendly, cooperative, four physician group in south-central Idaho. 165-bed hospital with GE signa 1.5 tesla MR, GE 9800 quick CT, Acuson XP, and good technical staff. General Radiology including angio, interventional, and nuclear medicine. Good income and vacation schedule, one year to partnership. Nice community with extensive nearby skiing, hunting, fishing, etc. 80 miles from Sun Valley, four hours drive from Yellowstone. Send CV and references to Dr Evan Thomas, Southern Idaho Radiology, PO Box AB, Twin Falls, Idaho 83303.

CARDIOLOGIST, full-time BC/BE, invasive/non-invasive, inpatient/outpatient for practice at general hospital in association with two Cardiologists and five Internists leading to partnership. Excellent vacation schedule and competitive salary. Twenty-five minutes from San Francisco. Reply to San Mateo County Hospital, Attn: Mark Highman, MD, 222 W 39th Ave, San Mateo, CA 94403; (415) 573-3786.

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SOUTHERN CALIFORNIA. Opportunity for part-time Emergency/Family Practice physicians at urgent care/industrial center in Orange. Send CV to Front Line Community Physicians, PO Box 10610, Santa Ana, CA 92711, or contact Medical Director at (714) 771-3290.

CLINICAL DIRECTOR FOR LOCAL ALCOHOLIC RECEPTION AND TREATMENT CENTER. Phoenix, Arizona. Seeking Clinical Director for local alcoholic reception and recovery center to join association of 70 providers, 18 clinics county-wide. Work 40 hours per week, five weeks vacation, one week CME, malpractice/disability/medical insurance paid. Competitive salary. Contact Norma Travis, Administrator, 2516 E. University, Ste 130, Phoenix, AZ 85034.

SONOMA WINE COUNTRY. Excellent Internal Medicine opportunity. Take over existing practice; share office with associate. Finances negotiable. Salary if desired. Send CV to PO Box 1641, Sonoma, CA 95476.

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SAN DIEGO COUNTY. Family, Internal, OB/GYN, and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

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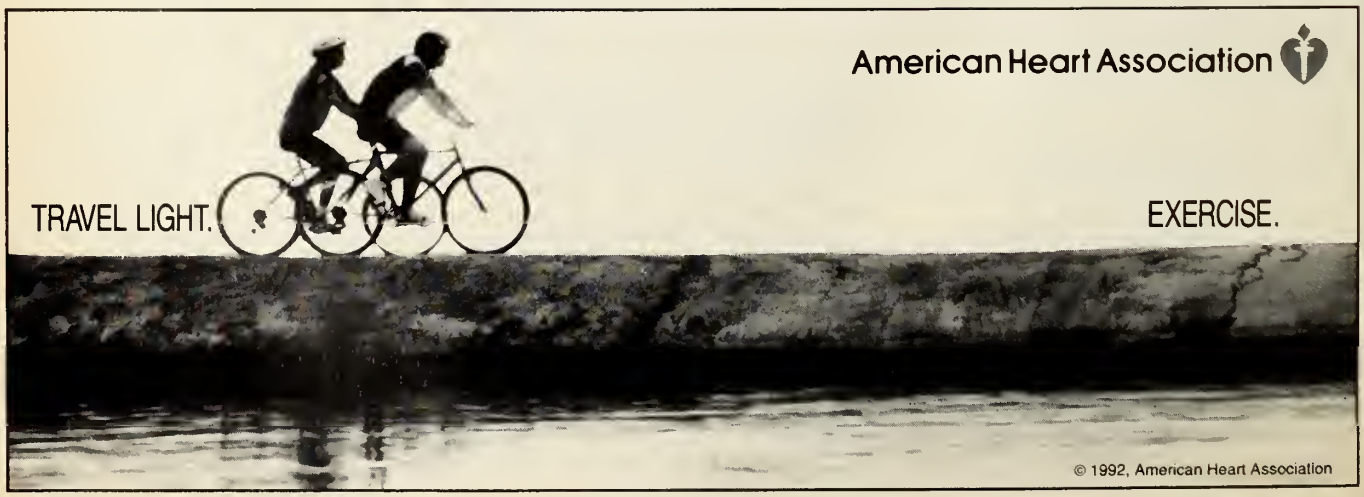

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: February 26-March 3, 1993, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-13, 1992, Copper Mountain.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1992, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 30-August 1, 1992, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 1-3, 1992, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1993, date and place to be announced.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1993, date and place to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): November 6-8, 1992, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. September 16-19, 1992, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: October 1-4, 1992, Yakima.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1993, date and place to be announced.

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